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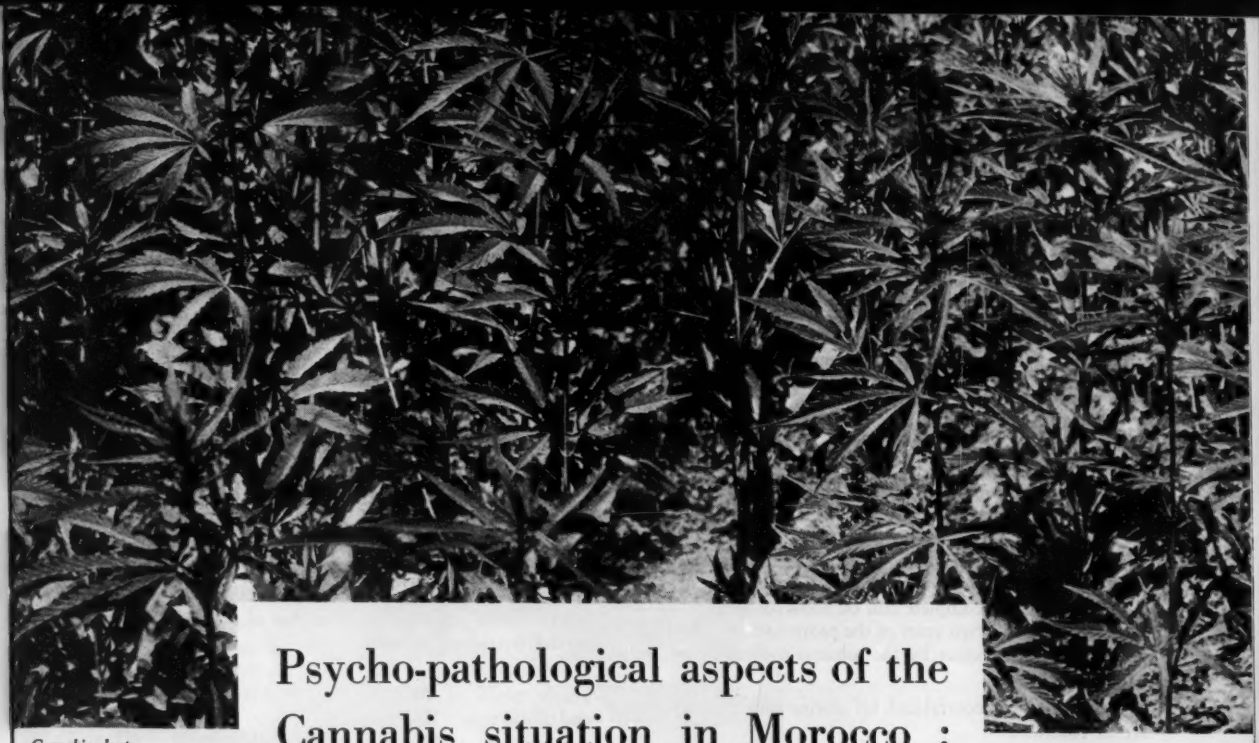

Cannabis plants

Psycho-pathological aspects of the Cannabis situation in Morocco : Statistical data for 1956

Report transmitted by the observer for Morocco, Dr. Ahmed Benabud, at the twelfth session of the Commission on Narcotic Drugs

I. The cannabis problem in Morocco

A. Historical Background

It is impossible to state accurately the date when cannabis was first used in Morocco. Known to antiquity, *Cannabis sativa L.* seems to have originated in central Asia, whence in remote times it spread east to China and west to Euro-Africa and, in particular, to the countries of the Mediterranean basin. Used in the ancient world for its textile fibres and oil seeds (hemp-seeds), its inebriating properties were for a long time restricted to the esoteric practices of different religions. Subsequently, and before it became a widespread general inebriant, it was used for its therapeutic properties.

In the fifth century B.C., the Zend Avesta mentioned the physiological effects of the resin and the flowering tops of the plant. In the seventh century A.D., originating in Persia and propagated by the Arab invasions, the use of cannabis spread to Syria and Egypt, the three Moghreb countries and Spain. Well-known Arab doctors such as Ibn Djezha, Al-Awan and Ibn-El-Beythar used it as a medicament under the names of konnab, hashish and fokkra (a reminder, subsequently forgotten, of the Indian origin of the plant).

The use of hashish as an intoxicant must have spread rapidly, and with dangerous consequences, among the mass of the peoples of North Africa, because from the eleventh to the fifteenth century the reaction of sultans and emirs was to inflict severe physical punishment (extraction of teeth, imprisonnment and even the death penalty) in cases of abuse of cannabis.

In the sixteenth century, Alpunis mentions that in Egypt the common people, and also those of the wealthy classes, sought inebriation by smoking assis and eating bers, magi-oun and pills of opium, cannabis and datura.

The first descriptions of the physical and mental deterioration caused by cannabis addiction, which they stated to be widespread, were brought back by the doctors of Bonaparte's expedition to Egypt, and the wars of the conquest of Algeria provided similar information.

In Morocco, Army doctors and, later, medical health officers, frequently took an interest in the cannabis problem. The first official measures, however, were exclusively commercial : the Algeciras Act had already granted to a company the monopoly of the manufacture and sale of kif, as of tobacco. The aim of subsequent *dahirs* regulating the cultivation, transport, sale and consumption of kif was the exclusive protection of the interests of the monopoly against clandestine producers and sellers (*dahir* of 4 May 1915 repressing smuggling — i.e., extra-monopoly trade).

In 1926, a zone of toleration to the north of Fez was set up in order to allow the adaptation to the new economic order of tribes which had recently submitted. That zone was gradually reduced until, in theory, it was abolished in 1929, although in fact, production continued at a high level, particularly during the last few years of the protectorate. The main economic problem of substitution of other crops — an essential prerequisite of any really effective

suppression of cannabis-addiction — was in practice never solved.

In the early days, the monopoly manufactured in Tangier chopped hashish (n'rama), which in 1932 was replaced by the jyed kif prepared at Port-Lyautey — a mixture of kif and tobacco in fixed proportions, that of pure kif ktami (tedrika) being 33%. Although, at the request of the Director of Public Health, in order to mitigate the toxic properties of the mixture, this figure was reduced to 20%, from the moral and health point of view this manufacture legalized use of kif.

However, the suppression of the sale of extra-monopoly kif was effectively carried out with the aid of heavy fines, without suspension of sentence, and even of imprisonment, which was authorized where necessary.

In 1940, the monopoly lost its privileges in the Spanish Zone and in the International Zone. The Spaniards permitted the cultivation of kif, which became quite an important source of revenue in their zone. The contraband trade, with a powerful organization, grew rapidly from year to year and, owing to the complete ban on tobacco, was particularly rife during the last two years of the protectorate. The figures provided in this respect by the tobacco monopoly are most revealing.

The seizures of contraband kif during the past ten years are as follows :

Year	*Weight* (Kilogrammes)	*Year*	*Weight* (Kilogrammes)
1946	5,700	1952	18,800
1947	4,987	1953	18,625
1948	8,800	1954	15,560
1949	7,650	1955	30,700
1950	8,125	1956	7,100
1951	16,000	January 1957	1,005

It is to be remarked that, although the volume of seizures doubled between 1954 and 1955, since 1954 the monopoly has received only a proportion of such seizures (*dahir* on the prohibition of kif hemp). Although the sherifian Government propaganda had some effect on the consumption of kif, the reduction by four-fifths in 1956 does not seem to indicate any sharp decrease in the trade.

The regular and large increase in the use of kif is none the less striking, as seen from a study of the figures of production and sales of jyed kif for 1943 to 1953.

Year	*Weight* (Kilogrammes)	*Year*	*Weight* (Kilogrammes)
1943	20,234	1949	48,080
1944	19,271	1950	57,013
1945	19,041	1951	55,456
1946	21,581	1952	46,521
1947	31,057	1953 (First three months)	10,211
1948	17,711		

Sales ceased on the publication of the 1953 *dahir*.

Pharmaceutical preparations with a cannabis basis are under international control on the basis of a recommendation made by the Health Committee of the League of Nations. The World Health Organization took a stronger line. In its view the use of cannabis for medical purposes was obsolete, and it recommended discontinuance.

The *dahir* of 24 April 1954 confirmed the abolition of the manufacture and official sale of kif and prohibited its production, sale and consumption. Shortly afterwards, cannabis was withdrawn from the French Pharmacopoeia.

The struggle against smuggling, which was principally aimed at protecting the monopoly's interests, however, came to an abrupt stop, and there was a marked increase in contraband trade.

To the figures both for seizures and illegal consumption, which showed a large and steady increase in the use of kif, must be added the number of cases admitted at the neuro-psychiatric hospital at Berrechid, a large majority of whom were suffering from cannabis psychosis. The number of hospital cases rose from 460 in 1946 to 1,850 in 1957. The number of patients treated (2,797 for the period 1936-1946) rose to 7,323 for the last five years alone, and at present cannot be far off 10,000, bearing in mind the work of the urban psychiatry services which have been started in the last few years. It would certainly be an exaggeration to suggest cannabis addiction as the sole explanation of this increase in hospital cases; it is, however, interesting to compare the annual graph of seizures of kif, month by month, which hardly varies year by year from that of cannabis cases treated at the Berrechid hospital.

With hardly any divergence, there are the three usual yearly peaks of March-April, August-September and the end of the year. That similarity is unlikely to be a chance one.

To sum up, in Morocco, cannabis addiction is of extremely ancient origin, vigorously combated by successive governments, but always spreading again as soon as there is a weakening of prohibition. In former times, when serious endemic disease was common, cannabis addiction was not regarded as a major social scourge, and by comparison with others, such as alcohol and opium, it does not appear to be the most pernicious. Today, however, two factors justify stress being laid on the problem. In the first place, there is the appreciable, and even considerable, increase — borne out by different statistics — in the use of kif, particularly among the urban industrial neoproletariat, where its effects are often aggravated by associated alcoholism; secondly, the disappearance of major endemic diseases, such as typhus and malaria, and the decrease in serious social scourges, such as syphilis and tuberculosis, which allows Morocco to tackle the public health problems met with in the highly developed countries — e.g., those of nutrition, psychiatry and mental health, and in particular those concerning drug addiction.

B. Present State of the Problem

The action taken by the sherifian Government, and in particular by the Ministry of Health, at the end of 1955 and during the first half of 1956 to warn the Moroccan public, through the press, broadcasting and even the cinema, against the abuse of kif, resulted in what was probably a considerable decrease in cannabis addiction. In any case, for seven or eight months there was a definite falling-off in the number of cannabis psychosis cases treated in the hospital at Berrechid; but the number of such cases again rose rapidly in the summer, and reached a peak in September-October 1956.

The problem of crop substitution, already mentioned, should be the first to be solved; the next step will be the launching of a publicity campaign which, in view of the definite public desire to co-operate, should be successful.

However, ktami kif is still widely cultivated in the Tetuan region and in the Rif, where thousands of people depend

Kif smokers

Kif smokers

for their living on its production. In the southern Atlas region and the Moroccan Sahara, there is general cultivation, even by the best families, of the zerouali, soussi, gnaoui, haouzi (sadda, teloeut) and makhlif (Ait makhlif) varieties of kif. There seems to be a tendency among the wealthier classes to smoke it, often for snobbish reasons. Cannabis addiction among females has also appreciably increased in recent years. Whereas previously the hospital cases were almost entirely confined to prostitutes, who smoked kif, and even opium in the company of soldiers, this year a few women from the middle classes were admitted for treatment.

Nevertheless, cannabis addiction is found mainly among the poorest classes; and cannabis takes the place of the pain-relieving aspirin; of a "comforting and strength-giving" litre of wine and even of an aphrodisiac. The use of cannabis has become so widespread in the last few years that the number of occasional or regular smokers has been estimated at nearly one million, a figure which has certainly fallen recently. It may be taken, therefore, that the number of smokers suffering from recurrent mental derangement is relatively very low, not amounting to more than five per thousand, a fact which illustrates the mildness of cannabis as compared, for instance, with opium. These figures, of course, include not only patients treated at the Berrechid neuro-psychiatric hospital and by the urban psychiatry services, but also all those with brief oneiritic-aberrational periods following cannabis inebriation, who are generally cured in from one to three weeks. It will be seen that the average period of hospital treatment, both by the urban services and at Berrechid, is not more than six weeks for the majority of acute cannabis psychotics of the aberrational type.

Kif smoker filling his pipe

C. Influence of Cannabis Addiction on the Number of Admissions to Hospital (mental cases)

The Ministry of Health, which is giving all the attention required to the problem of psychiatric treatment, is at present building up a system of psychiatric hospital services in each of the large towns of Morocco, each with sixty to eighty beds, for active psychiatric therapy under the direction of a qualified psychiatrist. These services are particularly suitable for the treatment of the very frequent cases of curable acute cannabis-psychosis of the oneiritic-aberrational type.

In the Berrechid hospital, in 1955, the number of genuine cannabis psychotics was 239 out of 1,017 male Moslem patients admitted; 72% of those admitted had to some extent been kif smokers.

In 1956, the figure fell to 68%, but the number of genuine cannabis psychosis cases was 328 out of 1,252 male Moslems admitted, which conceals a relative reduction — particularly marked at the beginning of the year.

The precise nature of cannabis addiction as a factor of admission to hospital will be examined in detail in the clinical study, but it was desirable to insist at the outset on the importance of this question in connexion with psychiatric treatment.

It is to be noted that, owing to the various types of treatment (sleep and electroplexy combined), withdrawal of the drug together with treatment of deficiency diseases and nutritional troubles (apomorphine cure), the number of socially rehabilitated cases is considerable and the number of chronic cannabis psychotics comparatively low.

II. Statistical data for 1956

A. Methods of Inquiry

The basis taken was the clinical observation of the 1,252 male Moslems admitted in 1956 to the Berrechid neuro-psychiatric hospital, the number of cases of female cannabis addiction — fifteen — being insignificant. A systematic breakdown of the observations was made using a roneoed card containing as full particulars as possible in each case, a model of which is annexed (see page 16).

One thousand, two hundred and three files were used as providing adequate data. In 824 cases, or 68% of those admitted, kif had been used, either regularly or occasionally. The re-classification and comparison of the different elements included enabled a number of tables and graphs, providing interesting statistical information, to be prepared.

B. Degree of Accuracy of the Data

It must be pointed out that there are a certain number of factors giving rise to inaccuracies which must not be overlooked in any appreciation of the results of this study.

1. Certain of these factors arise from the present state of psychiatric assistance in Morocco. Until a few years ago, Berrechid hospital had mainly served the region and town of Casablanca. Economic and social progress has

Cannabis field in the Rif

led to increased demands for psychiatric treatment throughout Morocco, necessitating the setting-up of psychiatric services in the large towns, which from the outset were compelled to deal with a large number of cases.

Thus the Berrechid hospital cannot treat a homogeneous group of patients as in a French departmental psychiatric hospital, where patients from all over the department attend regularly and in the same numbers.

In Morocco, certain regions — such as the extreme south — send only dangerous anti-social cases, whereas others — such as the Rif — are only just beginning to use the hospital services. Elsewhere, on the other hand, such as in Casablanca, there are the same criteria for admission to the hospital as in a French town, and a considerable number of patients therefore come from that city.

Thus in the seriousness and long-standing nature of their illnesses and in their ethnic and social origin, there is among our patients a very great diversity, which does not help the establishment of homogeneous statistics.

2. Further, there are not the same facilities for treatment in the different urban services. At the present moment, for instance, Casablanca is acting purely as a clearing-house, sending to Berrechid four-fifths of the cases admitted, whereas Marrakesh can deal with four-fifths of its cases locally and sends only one-fifth. (Since most acute cannabis psychotics are treated in Marrakesh itself, the figures for this region are deceptively low.)

3. Lastly, statistical research among the Moroccan people meets with a certain indifference towards accurate research into anamnesis. Population movements, the instability of residence, occupation and marriage all make the accurate docketing of the patient a difficult task.

On the other hand, some factors facilitate statistical work. Most of the patients, being penniless and therefore mentally backward owing to lack of education and the crippling worries of a hard life, live in a world without many complexities. Their reactions to the toxic effects of cannabis addiction will consequently be of little variety, and the symptomatology is generally restricted. That fact has made possible the statistical simplification of the table " Clinical classification ", which has been reduced to a few of the commonest syndromes.

III. Sociological and socio-pathological study

A. Demographic data

A brief summary of the demographic background of cannabis addiction is now called for.

In Morocco, out of a population of approximately 9,300,000 there are 8,700,000 Moslems, 400,000 Europeans and 220,000 Jews. Of the 8,700,000 Moroccans, 80% are country dwellers, of whom four-fifths are farmers, forest-workers or fishermen, most of the remainder being traders.

The Moslem urban population group, living for the most part in seven large towns, consists of 1,900,000 persons, of whom 550,000 (according to some authorities 600,000 to 700,000) live in Casablanca. In view of the wide population movements, particularly the regular drift of country people to the towns — which increases in years of bad harvests — and the difficulties of census-taking in the *derbs* and the shanty towns, the exact figure cannot be given.

Professor Montagne has estimated at 700,000 the size of the urban neo-proletariat, most of whom have come from rural areas to the large towns within the last fifteen years, over half of whom (400,000) are said to live in Casablanca. The capital importance of this neo-proletariat in the spread of cannabis addiction will be seen; it is such that the sociological study of cannabis addiction generally has as its subject the Casablanca neo-proletariat, because it is typical and forms a majority.

Although kif-addiction is widespread in country districts, it is mainly found among moderate smokers, who smoke only at work, in order to keep up their spirits, or as a relaxation. Cannabis addiction there shows no signs of being a compulsive need, and is different from that *mass addiction* found among the urban proletariat. As the country saying goes, " A little kif warms; a lot burns."

Moreover, the countrymen, who are socially better integrated (because of family, tribal and religious influences), seem to have a much stronger psychical resistance to the drug. The index " number of cannabis psychotics compared with the number of smokers " is estimated at about one-tenth of the figure among the Casablanca proletariat.

Out of 1,250 male Moslem cases admitted in 1956 to the neuro-psychiatric hospital at Berrechid, of whom 68% were kif smokers, — for a total population of 8,700,000 — more than half (639, 78% of whom were kif smokers) came from the Casablanca proletariat, numbering approximately 400,000 persons — i.e., these included twenty-one times the number of patients in the other population groups. When allowance is made, however, for the large number of cannabis psychotics treated by the urban services (Marrakesh, Rabat, Fez, Oujda) and violent cases of kif-smoking cured after a short spell in the Marabouts — whereas four-fifths of the Casablanca cannabis psychotics are directly evacuated to Berrechid — this figure must be reduced to about ten times, which is none the less highly significant.

B. Cannabis Addiction as a Mass Intoxication

Mass addiction in its most pronounced form is found in Casablanca.

As will be seen from the statistics, there is an obvious homogeneity in this neo-proletariat of rural origin, for the most part Berbers with scanty means, in small jobs which are uncertain and changing, wretched food and housing and who, moreover, have no future to look forward to. It is among these people that the use of kif has become widespread, often being taken in considerable quantities, which upsets still more the balance of consumption : irregular and hopelessly inadequate budgets are further burdened by the relatively high cost of kif, which is expensive compared with the general cost of living (2,000 francs per kilo wholesale, but a daily expenditure of 152-200 francs being quite normal).

Addiction has taken a firm hold in this class which is narrow-minded, highly suggestible, with a tendency towards compulsive imitation and always on the verge of an ever deeper frustration in an atmosphere of endemic poverty. Encouraged by tradition, by the therapeutic, strength-giving and tonic properties of the drug, by its innocuousness — which have always been acknowledged — the kif-smoking habit has become an essential part of the personality of the smoker like the daily three litres of wine in certain French proletarian circles.

This mass addiction seems to have such clear characteristics and to be set against such a definite background that it seems justifiable to speak of a veritable socio-genesis of cannabis addiction. The same situation in the other large towns of Morocco and in those areas in the process of industrialization can be compared with the type of addiction in the country districts, which, though endemic, has far fewer psycho-pathological consequences. Cannabis addiction is certainly prevalent there, as among the wealthier classes, where mahjoune, chira and kif (even kif mixed with small sandalwood shavings) are used. But the man in easy circumstances, and even the ordinary farmer with a few animals and a small holding, does not indulge in the kind of drug suicide met with among the uprooted and poverty-stricken proletariat of the large towns.

C. Close Relationship between the Inebriant and Ethnic Morphology

The view may be held without exaggeration that the people of every country have a pronounced weakness for one type of addiction, based on fundamental social aspirations as old as mankind itself, and that the choice of the drug is not prompted by chance or by cultural or economic opportunity, but on the contrary corresponds to a congruence between the effects of the drug and certain constitutional compulsive characteristics of the individuals who indulge in it.

Thus, there is an obvious relationship between the European, whose characteristic psychological structure is psychical extroversion, a psychothymic dynamism prompting him to immediate action and the challenge of his environment, and alcohol, which releases active and — on occasion — destructive impulses, aggressiveness and the will to power. In the same way, the schizothymic, introverted and contemplative temperament of the Far East is stimulated by the corresponding properties of opium.

In Morocco, drug addiction seems to induce in the smoker a psychomotor exaltation and an exuberance that cut through the family frustrations and taboos which may be particularly oppressive in Moslem society. The Moroccan, who is normally a visually imaginative person, naturally argumentative, with

feelings (often tinged with mysticism and intimations of the supernatural) that may be collectively shared and an emotional love of gesture sometimes expressed in a theatrical manner, may, through kif, give rein to these profound tendencies, for the drug stimulates oneiritic imagery, amplifies emotional overtones and facilitates the kind of collective "osmosis" characteristic of smoking parties. These parties are usually accompanied by interminable, blissful and friendly word-spinning, but not infrequently, after a few pipes, a mood of resigned akinesia will give place to impulsive release in action.

D. National Personality Characteristics as Toxicophilic Factors

Apart from individual cases, clinical observation among the most backward classes has enabled certain characteristic features predisposing them to addiction to be singled out. In particular, those people newly come to the city show a structural weakness of the ego, which is no longer buttressed by traditional custom; moreover, they have not received an adequate intellectual and moral training.

Hence, the mental attitudes and behaviour usual in the emotionally immature are extremely common — prevalence of the imaginary over the real, of the present over the future, with the impulsive need of the habitually frustrated for the immediate satisfaction of desire.

All those circumstances encourage the general and excessive use of the drug, in addition to a certain indifference on the part of the individual to his own fate, to the space/time details of his existence, and to the long-term consequences of his actions. The idea of responsibility towards oneself and others, which depends on the individual's degree of emotional maturity, is frequently insufficiently developed among the Moroccan proletariat, who generally prefer to fall back on symbolic interpretations and notions of magical possession and sorcery.

The importance of collective impulsive action, which is the outlet for individual weakness of the personality, is again to be noted. Mental transmission and mimesis, together with proselytizing tendencies characteristic of smokers, further encourage drug addiction.

E. Factors arising out of Contemporary Socio-economic Development

There is no doubt that in certain areas present-day socio-economic developments have created an atmosphere favourable to the spread of drug addiction.

No further reference will be made to the industrialization of the large towns — and in particular the seaports — which in a few decades has confronted Morocco with the serious social problems found in England in the nineteenth century, but which here are complicated by rapid increase in population. The structure of the working population has undergone radical changes because of a steady and vast rural exodus (an annual increase of 5% of the population of the towns as against 2% of the total population), which has produced an unstable mass of people living on the edge of organized society, with no security in their lives, who are constantly and painfully made aware of the relative opulence of the European way of life, not only through the difference between the "European city" and the "Medina", but also through the cinema, the press and broadcasting.

The breakdown of the archaic tribal and family structures has encouraged family instability (2.7 marriages per female and 1.8 per male among the 50,000 inhabitants of Ben-M'Sick), while religious and moral principles have weakened.

The forced inactivity of the unemployed and of men without a regular occupation or in small jobs (cf. statistical tables) drive them to drug addiction. Malnutrition and the ensuing deficiency diseases also encourage the individual to seek in drugs — not only in kif, but also, as will be seen, frequently in alcohol — a substitute for food and a sedative for the pangs of hunger. It is natural that these undernourished persons should have a weakened resistance to intoxicants, which rapidly becomes a tyrannical and permanent addiction.

For such people, the use of drugs as a refuge against moral despair and hunger has become a necessary element in their lives.

F. Modes of Spread of Addiction

Casual drug-taking as part of an "initiation" or an isolated therapeutic experiment is the exception.

Stress must be laid on paroxystic abuse during feasts, for such occasions are both frequent and important in the life of Moroccans — even the poorest — which tends to make the consumption of food still more irregular. These abuses, however, like the heavy drinking which accompanies European festivities, appear to have pathological effects only among individuals already predisposed to them, as the simultaneous intake of food diminishes the toxicity of the drug. On the other hand, frequent abuse during the fasting period of Ramadan produces a definite annual peak in the admittances to the Berrechid Neuro-psychiatric Hospital for cannabis psychoses. Further, in addition to personal, emotional and occupational stress, there is social and political stress, which undoubtedly affects the consumption of kif, whether for the purpose of alleviating distress or as a means of celebration, and there was a sharp increase in the number of cannabis psychotics during the outburst of popular rejoicing in October and November of 1955.

In the spreading of addiction, the importance of the prejudice in favour of kif on account of its innocuousness, its curing of toothache, lumbago, cephalea, etc., must also be emphasized. Certain sects (Ait Saoua, Hamatcha) use its analgesic and stimulating effects in order to practise public self-mutilations, which can be of a striking nature and which further enhance the prestige of the drug. As for the inveterate smoker, friendly and talkative, he is regarded by the public with the same indulgence shown to the "soak" in western countries. Moreover, kif has the reputation (not upheld by the facts) of stimulating sexual powers, and it is used as an ingredient in certain recipes for reviving a flagging desire.

The extent of the kif distribution network and the large number of places where it is used facilitate the spread of addiction. Although the wholesalers with their bundles of kif are relatively few and far between, the number of small clandestine pedlars in the *soukes* or the street stalls is legion. They come under the category of persons in small jobs without regular income (discussed below), and are obviously more exposed than other people to the danger of addiction.

There is no need to dwell on the frequently described smoking parties, where five or six persons in a closed room — at the back of a café, a tailor's shop or a barber's — smoke a series of pipes with resultant progressive inebriation. These parties meet a profound need for friendly relaxation in the company of men, the strong homosexual element in the male psychical constitution sometimes finds release at them, and they are a comparatively common means of initiation of young people into drug taking.

Lastly, especially in urban circles, where less heed is paid to the Koranic principles, wine is often taken while smoking, particularly when the drug taking is inveterate, and moral anaesthesia most prononced. As to the other toxic associations (considered below), from the sociological point of view, the comparative frequency of carbon monoxide poisoning must be mentioned, for this is a real occupational hazard of the *ferranji*, the stokers in bakeries or in the *hamman*, who work in unhealthy conditions. These people take kif as a relief from persistent headaches and mental depression, a remedy which merely aggravates the intoxication. Mention must also be made of the poly-intoxication of soldiers drinking wine and smoking kif — and sometimes opium — which may lead to anti-social demonstrations, often serious; and, curiously enough, they show frequent psychotic reactions of the querulant type in connexion with their pension rights.

G. Individual Psycho-pathological Factors

Socio-genesis is obviously not the whole explanation, and predisponent mental structures are very common among smokers, in particular periodic compulsivity among those who are constitutionally epileptoid, cyclothymic or hypermotive, which drives them to paroxystic toxic abuse and to recidivism. These are the serious cases, indulging their anti-social impulses, which may be compared with the pathological alcoholic inebriation of Europeans. Forms of mixed intoxication of kif and alcohol are also frequent.

As in the case of alcohol, an inadequate basic personality is particularly frequent: mental debility (accompanied by dangerous suggestibility and imitation of amoral acts stimulated by the intoxication), and emotional immaturity (with a feeling of inferiority or masochistic aggressiveness), which leaves the individual defenceless against the temptation of drug addiction.

Moreover, a certain number of known psychopaths suffering from epilepsy, cranial traumatism or syphilitic or paludal infestation have a particularly sensitive reaction to drugs.

Lastly, it is well known that the prodromic period in schizophrenia is often characterized by incidental drug taking, which is both the effect and the cause of the disease.

Thus, the importance and the frequency of constitutional predisposition are clear, a fact which justifies the adaptation of the well-known saying, "You are a kif addict long before you smoke your first pipe."

There are also the family nature of certain constitutional types of addiction (in five years both a father and son have been under treatment for addiction and there have been nine cases of two brothers) and the craving for any drug whether it be kif, alcohol — and even opium — or datura, with the minor elements represented by tea and tobacco.

IV. General statistical data

The analysis of the cards on the annexed model of kif addiction cases admitted to hospital in 1956 gave the following statistical details :

Proportion of smokers : 68% of cases admitted (824 out of 1252).

(a) *Age*

The age curve shows :

1. A few very rare cases (4) of paroxystic incidents among children (12-15 years), all from Casablanca;

2. A high and broad peak between 30 and 35 years of age;

3. A rapid fall after 40, with a "plateau" at about 55 years of age.

(b) *Sex*

It has already been pointed out that the cases are almost entirely males. There were only fifteen cases of female cannabis addiction, of whom five were prostitutes but, on the other hand, three were women in comfortable circumstances.

(c) *Vital Statistics*

1. A striking feature is the large proportion of unmarried men or men separated from their wives (42%), which seems to correspond with pauperism (see the table on income: 52% without regular income). Many alcoholics are also unmarried, a fact frequently indicating inadequate social integration.

2. There is also a high percentage — 18% — of divorced persons (mainly from Casablanca) :

	Percentage
Married men	30
Widowers	4
Status undetermined	6

(d) *Means*

Without regular income	52
Income of 10,000-15,000 francs (monthly)	23
Income of 15,000-20,000 francs (monthly)	16
Income of over 20,000 francs (monthly)	9

Since the average annual income of a Moroccan family is about 200,000 francs, the majority of patients, falling appreciably below that level, are in the poorest stratum of the population. Moreover out of 1,410 Moroccan Moslem hospital cases, there are 1,111 needy persons in the care of the Welfare Service, only 28 of whom can afford to pay hospital expenses. The point must be stressed, therefore, that it is precisely the poorest budgets which are further burdened by expensive purchases of kif. This explains the many examples in the case histories of broken families and abandoned children caused by addiction.

(e) *Housing*

Under this item, inaccurate replies were common, because many patients appear to attach little importance to settled dwelling : 35% live in shanty-towns, in the towns or in

noualla in the country districts; 52% live in houses in the *medinas* of the large cities and small towns; 11% have no fixed residence; 2% are nomadic shepherds (Berbers from central Morocco or Arab-Berbers from the extreme south-west).

Mention must be made of the patients' reports of the particular incidence of overcrowding in the houses of the *medinas*, with the result that they seem less healthy and more pathogenic than the shanty-towns. The proportion of shanty-town dwellers compared with those in stone buildings is obviously much higher in Casablanca than in other cities. Finally, there is the frequent impermanency of lodging : during the year preceding their admittance to hospital, about 30% of patients had changed their residence or their town more than twice.

(f) *Place of Origin*

The statistics have been established by province, large city, small town and *bled*.

Distribution by province	*Percentage*
Province of Casablanca	57
Province of Rabat	10.5
Province of Marrakesh	7.5
Province of Meknès	5.8
Province of Fez	2.3
Province of Tangier	4.4
Others	11.6

The results show :

1. The great importance in this respect of Casablanca, which sends 47.5% (53%, if the 5.5% of those without fixed residence from Casablanca are included). If Casablanca (550,000 inhabitants) is compared with the whole of the six other large cities (with a total of 1,900,000 inhabitants), the proportion is even greater, amounting to 68%.

However, it has already been pointed out that Rabat, Marrakesh, Fez, and Oujda have psychiatric services treating curable acute psychoses — usually cannabis cases — which are therefore not included in the Berrechid statistics. On the other hand, Casablanca, which is merely a clearing-house, sends almost all such cases to Berrechid.

2. A majority of town dwellers : 63% of patients come from the seven largest cities; 12% come from small towns of less than 20,000 inhabitants; 11% have no fixed residence, half of whom come from Casablanca.

3. Country districts provide only 14% of patients (of whom scarcely two-thirds are farmers).

These figures confirm what has already been said of the importance of cannabis addiction among the urban neo-proletariat and its comparative infrequency in the country districts (however, the well known indulgence of the tribes towards mental cases must be stressed).

It should be noted, however, that the proportion of unmarried men and men separated or divorced from their wives is much larger in Casablanca.

(g) *Occupation*

The striking feature here is the large number of patients *without regular means of support*, representing 60% of the cases admitted, broken down as follows : (1) No regular occupation, 47%; (2) unemployed, 39%; (3) casual labour or persons without qualifications in small jobs (water-sellers, skewered-meat-sellers, cigarette and kif vendors, bootblacks, beggars, etc.), 14%. The proportion of *workers* is 17%, composed of : Labourers, 35%; comparatively skilled workers in regular employment (bakers, masons, dockers, chauffeurs). 53%; genuinely skilled workers (mechanics, welders), 12%.

The proportion in *agricultural occupations* is 10% (*rhames* [*share-croppers*], small farmers, shepherds).

Note that one-third of the patients from the country districts are not farmers, but traders and persons not in regular employment, etc.

The proportion of *craftsmen* (tailors, cobblers, carpenters, barbers — whose shop is often used for smoking) is 6%.

The proportion of *traders* is 3%.

The proportion of *civil servants* is 2% (with a high percentage of *moghaznis*, policemen, railwaymen and postal employees).

A balance of 2% gave no particulars.

It is interesting to compare these figures with those given by the general statistics of Morocco as regards distribution in the three sectors of economic activity :

	Total population	*Hospital cases*
	(Percentage)	
Primary activities (agriculture and mines)	72	10
Secondary activities (industry)	18	17
Tertiary activities (trade and services)	10	5

V. Clinical study

A. Methods of Intoxication

(a) *Drugs*

The commonest drug is cheap kif, deficient in active properties and mixed with tobacco in varying proportions. One out of four addicts have also consumed cannabis preparations in the form of a paste or a decoction. The average number of pipes smoked is between twenty and thirty daily, but figures of forty to fifty are not infrequent. The cost varies between 100 and 400 francs a day.

(b) *Associated Intoxicants*

The main intoxicant is obviously alcohol, the frequency of which is seen in the annexed statistical table. It is usually combined with kif smoking. The consumption of large quantities of cold tea (*deka*) or coffee is an additional stimulant, which is sometimes by no means negligible. The combination of cannabis and datura or belladonna may be much more serious, for it induces a state of either acute rage or stupor, but it is rare. Mention has been made of some cases of the kif-opium association among former soldiers.

(c) *The Pattern of Intoxication*

The duration of the addiction has often to be taken into account; some patients had already begun to smoke at fifteen years of age. However, the important fact is that cannabis addiction is not marked by the progressively increased

consumption characteristic of more serious drug addiction. Habituation is hardly appreciable, and only about one-third of the patients are regular smokers. Withdrawal is not usually followed by psychic or somatic effects.

Occasional smokers have psychopathic reactions only when there is a considerable basic psycho-pathological element. In such cases, there is pathological inebriation, and with certain patients the threshold of excitation and oneirism is reached at a very early stage.

The most typical feature of the addiction is its paroxystic character. The uncertainty of supplies and of funds available encourage irregularity of consumption. Smoking takes place particularly among friends and people of the same occupation and on occasions for rejoicing or at feast times. The craving becomes paroxystic and there is massive intoxication. Most acute attacks begin in this manner.

(d) *Duration of Treatment at Berrechid*

The table in the annex gives the following groups : 50% of patients are in hospital for under three months; 30% are in hospital for under one year; 20% are in hospital for over one year.

The average length of the first period in hospital is forty days. The over-all proportion of relapses is one-third, and the second period lasts on an average fifty-two days. One in ten patients suffers two or more relapses, the repetition of the treatment being due to psychoses of varying origins in which drug addiction is merely an element. Such psychoses constitute almost the entire number of relapses after the third period of treatment.

60% of cannabis psychotics leave hospital before the end of three months and 40% after three months, whereas in cases of psychoses of varying origins in which drug addiction is merely an element, the proportion is reversed, 40% leaving before the end of three months, and 60% after three months.

The duration of these psychoses varies considerably; some, in which the incidence of cannabis predominates, being of very short duration, and others — the serious psychoses, in which intoxication is merely an accessory cause of aggravation — being fairly prolonged.

Cases of toxi-infectious psychosis, which are serious on account of the association of several etiological factors, form the largest number of admittances, remain for the longest periods, and show the highest mortality (6.8%). On the other hand, there are few relapses in this group.

Cases of psychosis with a cannabis element only show the lowest death rate (2.9%). The general mortality rate of the hospital is 8% of admittances, and the general mortality among cannabis cases is only 4% (the majority of patients being young, serious somatic effects are relatively rare).

B. General Character of Psycho-pathological Reactions in Moroccan Society, with Particular Reference to Cannabis Addiction.

The general reaction of the Moroccan psychical constitution to morbid processes of whatever origin must first be made clear. It will be seen that, whatever the etiology, there is a certain definite similarity in the general features of these Moroccan defence reactions. In particular, cannabis intoxication does not appear to cause any specific reactions.

Generally speaking, therefore, and whatever the nature of the morbid trauma, the mental defence reaction of backward Moroccans is a progressive and lasting stupor, the elements of which are psychological withdrawal, mental inertia, lack of interest in the surroundings, and a kind of intellectual hibernation, which may be regarded as dementia, but can be completely cured, sometimes after several years. These defence reactions are very different from those of the European, whose resistance to mental disease usually takes the form of a multiplication of delirious patterns or of positive reactions, giving place to dementia — which is then chronic — as the unfortunate conclusion of a prolonged struggle. The Moroccan seems to range time on his side, husbands his strength and, armed with patience, solves the problem by the supernatural explanations so frequently heard on the lips of our patients.

There is, moreover, a fairly widespread thymo-emotional instability, in which short, sharp and violent reactions, not produced by formal mental processes, predominate. The victims of this instability are at the mercy of the slightest trauma, particularly of a toxic nature, but, as will be seen, the trouble usually passes quickly.

It is a quite common psychiatric experience to meet with phenomena of dissolution of consciousness accompanied by oneiritic states of imaginative repression which give the impression of a fundamental deterioration of the psychical pattern, whereas there is merely a temporary functional disturbance.

Lastly, there are repetitive tendencies — in particular, spectacular behaviour — and those of mental perseveration, which may be checked by counter-suggestion and carry no implications of stereotyped attitudes.

To a large extent, the root of all these phenomena, which are the most obvious features of our daily observation, is cannabis intoxication. However, one has the impression that in this respect the response of the psychical constitution to a particular trauma — of a toxic nature, for instance — is less specific than in other cases.

This explains the difficulties and the nature, sometimes rather artificial, of the clinical classification of cannabis cases (cf. statistical table annexed).

In short, there are many cases where a temporary or slight intoxication will have no effects and has no connexion with the mental disorder.

On the other hand, there are many genuine cannabis psychoses in which the role of the intoxicant is both obvious and exclusive, or, on occasion, is supplemented by another intoxication or some organic infection.

In other cases, the psychopathic structure will predominate, cannabis intoxication being merely an element which may have brought about a veritable mobilization of latent psychopathic elements, or — as sometimes with alcohol at the beginning of schizophrenia — may precipitate the development of the prodromic stage of a psychosis.

Further, and finally, the use of kif may merely aggravate a psychosis already developing independently (a toxic oneiritic-aberrational-syndrome aggravating, for instance, the development of epilepsy).

C. Clinical Aspects of Cannabis Psychoses

The detailed clinical study will be confined to the main cannabis psychoses, where the mental disorder is directly

conditioned by the intoxication, mental predisposition playing only a minor role.

Paroxystic manifestations taking the form of acute or sub-acute psychosis are by far the most frequent, and are often the first indication of derangement, which, however, is sufficiently serious to justify hospital treatment. This first stage may be succeeded by a more prolonged residual syndrome and a second attack often necessitates further treatment after a short period. Patients who have had several such acute attacks of intoxication often show some degree of psychological deficiency and even of physical deterioration.

(a) *Acute or Sub-acute Psychoses*

It has already been pointed out that certain subjects, owing to particular susceptibility, show signs of acute disturbance after very small doses of intoxicant. These cases should be compared with the pathological inebriation described in connexion with alcoholism. Generally speaking, these acute states, which are rarely produced by an intercurrent morbid condition, and still more rarely by withdrawal, occur as a reaction to a sharp toxic overdose. The acute stage usually lasts some days, being followed by a residual amnesia of the lacunary type and prolonged intellectual lethargy.

The main features of acute psychosis are excitation and an impulsivity liable to produce serious anti-social reactions (violence shown particularly towards the mother, the wife or the family, or against types of individuals who attract hostility for political or religious reasons).

There are also : phenomena of mental aberration showing every degree of complex, oneiritic and predominantly visual poly-hallucinatory states; disturbances of exteroceptory and proprioceptory categories, with a deterioration of the spatial faculty, which may cause a dissolution of the unity of the personality, and is accompanied by autoscopic phenomena not dissimilar to those found in certain psycho-motor paroxysms of temporal epilepsy. These phenomena of dissociation may also take the form of post-oneiritic ideas, when the patient persists in the conviction of the duality of an " actor-ego " and a " spectator-ego ". However, the atmosphere of oddity and fantasy characteristic of cannabis oneirism only rarely produces an anxiety reaction. There is a kind of detachment facilitating the thymic reactions that encourage recourse to frequent erotic or mystical " elements ", among which ideas of satisfaction or power, themes of greatness and kinship or identification with God, the Prophet or the Sultan are most frequent. Occupational themes are rare, except in cases of associated alcoholism or carbon monoxide intoxication. The frequent impulsivity seems to be linked with a constitutional pattern rather than to depend on oneiritic phenomena, and is similar to epileptoid reactions in its lack of motivation, the absurdity and sometimes the savagery of the acts committed, as if a breaking wave were to sweep over the consciousness, leaving behind it very often only an amnesia and indifference. These are mainly cases of aimless fugues, impulsion to destructive or homicidal acts, outbursts of pyromania, or sexual offences.

Depending on the dominant aspect and the intensity of the disturbance, three basic symptoms may be isolated : aberration, oneirism, and excitation, the clinical forms of which, in order of frequency, are : maniac-aberrational; oneiritic-aberrational; simple maniac; aberrational or catatonic stupor; simple intellectual obfuscation.

(b) *Residual Cannabis Psychoses*

These are prolonged psychical disturbances following a paroxysm, and are often similar to schizophrenia, chronic hallucinatory psychosis and even dementia. However, traces of oneiritic patterns supporting delirious beliefs are met with; these latter are blurred, scarcely expressed, irregular; and without any tendency to become organized and to proliferate as time goes by. On the contrary, they tend to become dim and to disappear after a few months. There are thus :

1. *Pseudo-dissociations*

In a young subject, towards the end of the initial stage, there is a condition of atypical depression with mimetic insufficiency, oddities of behaviour and an inability to face reality resembling schizophrenia; there is no genuine autism, but rather a sort of paralysis of the personality, leaving nevertheless some possibilities of contact with the outside world, a contact reflected in phenomena of passive, plastic suggestibility.

2. *Prolonged Aberrations*

There is persistent mental obfuscation, apathy and complete inactivity, whether accompanied or not by oneiritic phenomena.

An infectious additional factor (paludism, syphilis) is common in the etiology of these aberrational conditions. They may be interspersed with attacks of tremor, but often disappear after a few months.

3. *Hallucinatory Syndromes*

Hallucinatory pseudo-delirium may occur residually after the acute initial stage, but the themes of delirium are poor, without any imaginative or interpretative richness, and the absence of reactions on the part of the patient is more or less constant.

Auditive hallucinations take the form of insulting words, of invective of a religious or political character, or dealing with sexual taboos; they are stereotyped, varying little from one patient to another, and have an anonymous character, because of which the naming of the persecutors is rare.

(c) *Psychical Cannabis Deterioration*

This occurs in regular smokers to whom prolonged toxic impregnation imparts distinctive characteristics. These are the old addicts, exuberant, friendly, kif-happy vagabonds, often oddly dressed and living by begging.

Their decay — usually progressive — affects, first, their occupational capacity and then their family behaviour; a lowering of affectivity is soon accompanied by a weakening of the moral sense; temperamental disturbances are rarely pronounced and anti-social reactions of minor importance.

Physically, inveterate smokers suffer from a precocious senescence, which occurs sometimes in the forties.

The over-all deterioration of the faculties may be sufficiently serious to produce general paralysis, other symptoms of which may also be found, such as tremulation, dysarthria and vague and puerile ideas of supremacy.

(d) *Somatic Trauma*

Generally speaking, even when the condition is acute, serious somatic trauma is rarely met with, as in the case of

serious toxi-infectious syndromes. Neuro-vegetative derangement is usually not pronounced, and the prognosis *quoad vitam* favourable, except in the rare cases of a profound physical trauma caused by massive and prolonged intoxication or by an intercurrent infection.

Quite often the impregnation of the nervous system produces trembulation, either digital or lingual, which may even be generalized. Tendinous hyperreflexia is common, but the symptoms of the poly-neuritic series are exceptional, save in cases of associated alcoholic intoxication.

Cephalea, vertigo and insomnia are frequent, as are digestive troubles, loss of weight, subicterus, anorexia, constipation and dryness of the mucous membrane.

Visual trouble is also met with : amblyopia, myosis, decreased photo-motor reflex, retinitis.

Sexual impotence is practically the rule among aged smokers.

Special stress must be laid on deficiency troubles, both nutritional and toxic in origin, which are probably the cause of most nervous and mental derangement. And the prognosis or, at least, the rapid cure of cannabis intoxication, will often depend on their prompt treatment.

D. Anti-social Reactions

Cannabis intoxication is generally regarded as being at the root of derangement causing anti-social behaviour, withs a high medico-legal co-efficient.

Difficulties of occupational behaviour are common; idlenes seems to be the first consequence of drug-addiction, and is often accompanied by neglect of family duties.

In most addicts, there is a social degeneration which is mainly responsible for minor anti-social acts, such as disorderly behaviour, vagrancy, petty crime and moral depravity. Despite their frequency, acts of violence do not usually have serious consequences, and they are committed particularly against other members of the family.

The role of intoxication must be stressed in the origin of serious crime, such as arson, indecent assault and homicidal acts. For instance, among the in-patients, three-quarters of the criminal acts were committed in a state of semi-consciousness caused by the intoxicant. Such reactions usually take the form of a psychomotor paroxysm, but they appear to be conditioned rather by heightened constitutional impulsive tendencies rather than by oneirism, in which the thymo-affective element is not usually pronounced, except in the specific cases of additional alcoholic intoxication. Inebriation of the despair type is particularly frequent among isolated smokers, for isolation appears in addiction as a definite factor of pathological predisposition. Frequently, these persons are epileptics or schizophrenes, whose aggressive potentialities em to be aggravated.

Serious anti-social reactions show little variation in nature : there is a lack of precaution, with no premeditation, nor affective or concrete motivation, and frequently the victim is picked at random.

In most criminal acts, there is also an outstanding element of violence and persistence.

It is an interesting fact that there is a comparatively large proportion of incendiaries among cases of toxic psychosis. Suicide, a rare phenomenon in Moslem pathology, is found only among recognized psychopaths, whose mental derangement has been aggravated by drug addiction. Similarly, the proportion of homicidal reactions appears to be relatively greater in persons whose psychological pattern is stamped with definitively abnormal characteristics.

E. Psychoses with a Toxic Element

The part played by constitutional pattern or morbid predisposition in the birth of the kif smoker's mental derangement has been mentioned. The role of the intoxicant is essentially that of an element, either through the precipitation or mobilization of latent pathological states, or through the aggravation of the clinical symptoms or the development of constituted psychoses, features of which were already clearly determined.

(a) *Mobilized Psychoses*

These occur in patients whose mental derangement had usually remained in the sub-clinical stage. Intoxication introduces an acute stage, of which the main component is oneiritic-aberrational, during which symptoms of initial mental morbidity appear. The patient enters the active stage of his psychosis, which then seems to develop independently. This is the pattern of development of a certain number of schizophrenic psychoses, the delirious outbursts of degenerates and paranoiac psychotics.

(b) *Aggravated Psychoses*

Cannabis intoxication may change the behaviour of some recognized psychopaths, and in most cases there is a low threshold of toxic susceptibility.

Schizophrenic conditions show heightened impulsive tendencies, which are often responsible for acts of violence; the most characteristic complication is seen in catatonic attacks, and there are also hallucinatory delirious outbursts, which appear to affect the subsequent development of the disease.

Among intermittent smokers, toxic excess aggravates not only the frequency of the attacks, but also their symptomatology. Manic attacks are by far the most frequent, and there is always a more or less noticeable element of aberration and oneirism with considerable agitation.

Under the effects of intoxication, epileptics pass through acute psychopathic stages of the oneiritic-aberrational type or else hallucinatory delirious outbursts, and there is also a recrudescence of critical symptoms.

Cases of cranial traumatism are particularly sensitive to intoxicants. They may show symptoms of an epileptic type or oneiritic-aberrational attacks.

F. Cannabis Psychosis with a Toxi-infectious Element

In certain cases, the clinical pattern of cannabis-psychosis may be aggravated by a toxic or infectious association, the two commonest and most outstanding factors being alcoholic intoxication and evolutive syphilis.

The commonest clinical symptoms are represented by a serious oneiritic-aberrational condition, with strong somatic participation and an element of decompensation, which is unusual in straight cannabis paroxysms. In such cases, the mortality rate is definitely higher than in the other forms of intoxication. Alcoholic intoxication sometimes leads to disturbances of the poly-neurotic series.

VI. Conclusion

The consumption of kif in Morocco, which, liable to fairly wide fluctuations, had appreciably fallen at the end of 1955 and the beginning of 1956, has since then risen again — particularly in August, September and October 1956 — without, however, reaching the level which obtained prior to the government campaign.

From the psychiatric point of view — the approach which interests us — it would seem desirable to unify the anti-cannabis campaign by the following means :

(1) Better knowledge of the psychiatric and social aspects of cannabis addiction through the general use of a record card for drug-addict mental patients in the different psychiatric services. This could be similar to that used for the present psychiatric statistical enquiry;

(2) The establishment of a central card index for classifying data received, and acting upon the conclusions drawn;

(3) Standardization of the psychiatric and somatic treatment of drug addicts with a view to generalizing, by comparison of methods and results, the most effective methods of treatment; in particular, the correction of deficiency factors might be made on the basis of recent research and the immediate results available. Further use might also be made of conditioning treatments which, having been tested at Berrechid for two years, have already given highly satisfactory results;

(4) The extension in the large towns of psychiatric consultations for out-patients by qualified psychiatrists, which would allow a certain number of cases of intoxication to be detected before the appearance of serious mental derangement, the supervision of convalescent addicts, and the intensification of propaganda in circles from which addiction stems.

Since the socio-economic evolution of the country will inevitably entail an increase in mental disease every year, it is obviously more necessary than ever to reduce the incidence of cannabis addiction, thus relieving the pressure it exerts on hospital facilities.

VII. Annex

Anti-social reactions

Anti-social reactions	Specific cannabis psychoses	Psychoses with cannabis element	Cannabis psychoses with toxic-infectious element	Pure cannabis psychoses *Paroxystic symptoms*
Minor				
Disorderly behaviour	71	11	4	19
Violence	20	20	8	17
Anti-family reactions	10	4	1	11
Serious				
Arson	5	2	1	4
Violence	6	3	1	6
Attempted murder	4	5	0	3
Attempted suicide	—	2	—	—

Syphilitic infection associated with cannabis intoxication

(Percentages)

	Patients showing signs of cannabis intoxication	Acute specific cannabis psychoses	Cannabis psychoses with a toxi-infectious element	Psychoses with a cannabis element	Residual specific cannabis psychoses
B W	38.5	34	82	32	26
Syphilis not determined clinically. No effect on the psychosis	27.3	34	—	25	26
Humoral syphilis constituting an aggravation factor	8.5	—	82	—	—
Syphilitic meningo-encephalitis	2.7	—	—	7	—

Alcoholism and cannabis addiction

(Percentages)

	Association of alcoholism and cannabis-addiction	Determining alcohol factor in the origin of the derangement	Alcohol aggravation factor
Total patients showing signs of cannabis intoxication	25	6	—
Patients with paroxystic symptoms	30	21	—
Cannabis psychoses with a toxi-infectious element	50	50	—
Syphilitic cannabis psychoses	20	—	—
Total addicts from Casablanca	66	—	30

Patients from Casablanca

Clinical data	Percentage	Element of comparison
Kif smokers	78	Total admittances from Casablanca
Pure cannabis psychoses	66	Total cannabis psychosis in-patients
Specific cannabis psychoses	57	Total specific cannabis psychosis cases
Aggravated cannabis psychoses	79	Total aggravated cannabis psychosis cases
Psychoses with a cannabis element	50	Total psychoses with a cannabis element
Alcoholism	66	Total kif smoking alcoholics

Hospital treatment particulars

(Percentages)

	Patients showing physical and psychical signs of cannabis intoxication	Specific cannabis psychoses	Cannabis psychoses with a toxi-infectious element	Psychoses with a cannabis element
1st period	67	69	75.8	60
2nd period	23	25	13.7	24
3rd period	7.7	5.4	10.5	10
4th and subsequent periods	2.3	0.6	0	6
Under 3 months (1st period)	53	60	66	40
Over 3 months (1st period)	47	40	33	60
Average length of 1st period (days in hospital).	40	42	47	36
Average length of subsequent periods (days in hospital)	52	49	63	54
Deaths	4	4.3	6.8	2.9

Vital statistics

Family status	Casablanca	Rabat	Marrakesh	Fez	Meknes	Tangier	Other towns	Country districts	No fixed residence	Small villages	Total	No particulars
Unmarried or separated ...	96	26	8	3	13	17	6	30	27	23	249	
Married	81	18	3	—	7	6	5	25	2	25	172	
Divorced	49	13	2	—	5	—	3	15	18	7	112	
Widowers	10	3	—	—	1	—	—	3	5	3	25	
Status unknown	8	4	3	1	—	3	—	3	6	2	30	
TOTAL ...	244	64	16	4	26	26	14	76	58	60	588	10

Occupations

Occupation	Casablanca	Rabat	Marrakesh	Fez	Meknes	Tangier	Other towns	Country districts	No fixed residence	Small villages	Total	No particulars
Not in regular employment .	162	44	10	2	16	16	10	16	52	36	364	
Craftsmen	12	4	—	—	4	6	—	—	—	4	30	
Traders	4	0	—	—	2	2	2	—	—	4	14	
Civil servants	6	2	—	—	2	2	—	—	—	2	14	
Farmers	—	—	—	—	—	—	—	54	4	—	58	
Workers	40	10	6	—	2	—	2	6	2	12	80	
Labourers	20	4	—	2	—	—	—	—	—	2	28	
TOTAL ...	244	64	16	4	26	26	14	76	58	60	588	10

Statisties 1956, Admittances to the Berrechid Neuro-psychiatric Hospital

Clinical classification

Patients showing physical and psychical signs of cannabis intoxication : 49 %

Specific cannabis psychoses : 27 %

Acute or sub-acute syndromes : 20 %
- Aberrational : 8 %
- Oneiritic-aberrational : 8.6 %
- Excitation : 3.2 %
- Acute catatonia : 0.2 %

Associated psychoses. The intoxicant having no effects on the clinical aspect or on the development of the case : 19 %

Cannabis psychoses aggravated by a toxi-infectious element as a determining factor in the clinical aspect of the development of the case : 5 %

Residual syndromes : 4.5 %
- Prolonged aberration : 0.9 %
- Dissociation : 0.9 %
- Hallucinatory syndrome : 5.7 %

Deficiency syndromes : 2.5 %
- Psychical debilitation of the pseudo-P.G. type

Kif-smoking mental in-patients

Cannabis psychoses. Pure intoxication, non-determining mental pattern : 32 %

Mobilized psychoses. The toxic factor has a precipitating role in the development of the derangement : 6 %

Alcohol : 2.1 %

Humoral syphilis : 3.7 %

Other factors
- Paludism : 0.2 %
- Carbon monoxide
- Other intoxicants

Psychoses with a cannabis element. Psychopathic pattern predominant : 17 %

Aggravated psychoses. Normal evolutive psychopathic syndromes aggravated by intoxication : 11 %

Schizophrenic: 3 %
Delirious outbursts of the Magnan type : 2 %
Paranoiac psychosis : 1 %

Schizophrenia : 3.1 %
Intermittent psychosis : 3.1 %
Epilepsy : 1.6 %
Cranial traumatism : 0.7 %
General paralysis (paranoid delirium) : 1.4 %
Chronic hallucinatory psychosis : 1.2 %
Neurosis : 0.9 %

N B. : All percentages on the basis of annual admittances (Moroccan males : 1,252).

Statistical card for cannabis-addicted mental patients

Name ..... No. ..... Sex ..... Age .....
Date of admittance ..... Duration of treatment ..... Number and duration of previous treatments .....
Date of leaving .....

Reason for leaving ....
(1) Marked improvement or cure
(2) Average improvement : left at request of family
(3) Little improvement : left against medical advice
(4) Unauthorized
(5) Death

Family status .....
Unmarried
Married, divorced, widowed
Number of children maintained .....
Status undetermined

Origin .....
Large cities ..... Houses, shanty-towns, no fixed residence
Small towns ..... Houses, shanty-towns, no fixed residence
Country districts ..... Sedentary, nomad
No particulars

Occupation .....
None, unemployed, in small jobs (bootblack, waterseller, skewered-meat seller, newspaper seller, pedlar, porter, beggar, etc.)
Labourer, worker, skilled worker
Trader, craftsman, civil servant
Farmer
No particulars

Income:

Cannabis intoxication

Age at beginning .....
Pattern (occasional, intermittent, paroxystic, regular)
Quantity .....
Mode of consumption (smoking, eating, drinking kif, resin)
Associated intoxicant : Alcohol, tea, coffee, datura, carbon monoxide, opium

General organic condition

1. Associated infections : Tuberculosis, humoral syphilis (BW : .....), paludism, amoeba
2. Malnutrition — deficiency symptoms
3. Neurological symptoms of intoxication (insomnia, tremulation, amblyiopia)
4. Pulmonary or digestive attacks

Anti-social reactions

Vagrancy	Minor attacks of violence	Serious attacks of violence
Indecent exposure	Brawling	Murder or attempted murder
Larceny	Disorderly behaviour	Suicide or attempted suicide
Arson	Subversive acts	Rape

Clinical classification

Mental background	*Basic psychic syndromes*	*Predominating clinical feature*	*Development*	*Toxi-infectious etiologies*
1. Debility	1. Schizophrenic syndromes	1. Aberrational	1. Previous paroxystic (under 2 months)	1. Exclusively cannabis
2. Backwardness	2. Manic-depressive psychoses	2. Oneiritic-aberrational	2. Continuing paroxystic (under 6 months)	2. Partially cannabis
3. Instability	3. Delirium	3. Hallucinatory	3. Prolonged	3. Unconnected with present cannabis addiction
4. Pithiatism	4. Primitive mental aberration	4. Stuporous		4. Associated cannabis and alcohol
5. Hyper-emotivity	5. Epilepsy	5. Catatonic		5. Cannabis and carbon monoxide
6. Cyclothymia	6. General paralysis	6. Manic-hysteria		6. Cannabis, opium, datura, belladonna
7. Schizoidia	7. Senile and pre-senile dementia	7. Depressive		7. Syphilitic
8. Paranoic constitution	8. Toxi-infectious syndromes	8. Anxious		8. Paludal
	9. Poly-toxic syndromes			9. Amoebic
	10. Neuroses			10. Tubercular

Studies on cannabis obtained from hemp plants grown in Japan

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Introduction

Hemp plants grown in Japan have been demonstrated to be toxic by physiological tests on goldfish or dogs, but the physiologically active principle, presumably tetrahydrocannabinol, has not yet been isolated from it, and little is known to us about its content of active resin, although it is said to be less potent than the hemp grown in some other countries.

Among the identification tests usually employed for the identification of cannabis samples seized in the illicit traffic, the best-known chemical test, Beam's colour reaction, is not based on tetrahydrocannabinol, and the hemp of Japanese culture that we have examined so far gave a negative test with Beam's reagent.

A reliable forensic test merely to identify cannabis could be based on any chemically active compound uniquely characteristic of hemp; but any test to identify potent hemp or to assay the cannabis drug for potency still awaits discovery, and must be one given only by physiologically active components.

For the purpose of separating the active principles from cannabis of domestic origin and clarifying their properties, we have undertaken basic research on cannabis.

This investigation was supported in part by a grant in 1956 from the Welfare and Health Ministry.

The following topics were studied in this fiscal year : (1) Extraction of hemp tops; (2) Colour reactions of hemp extract; (3) Detection of cannabis components by paper chromatography; (4) Spectrophotometry of cannabis resin.

Extraction of Hemp Tops

At the time of flowering of the domestic hemp plants cultivated in 1956 at the Minami Oshihara Experimental Station of the Tochigi Prefectural Farm, the plants were cut one foot from the top, and the twigs and leaves were air-dried. They had no narcotic odour.

The extraction of the dried tops was carried out by courtesy of Dr. Nishizawa at the Tokyo Factory of the Takeda Pharmaceutical Industries, Ltd., according to the procedure devised by Mr. Takeuchi, chemist of that factory.

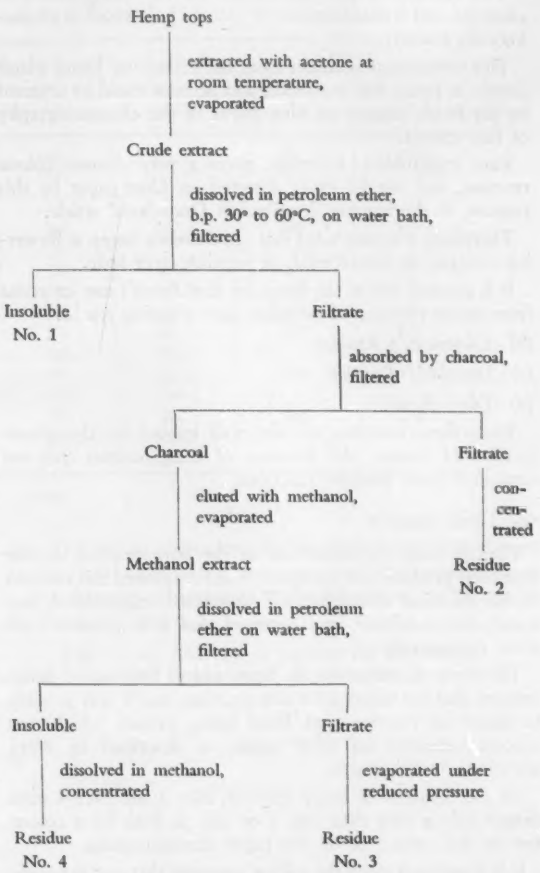
When 1 g. of the air-dried tops was cut into small pieces and dried at 105°C to constant weight, the loss of weight was 11.9%.

The principle of this extraction is to absorb the active components by charcoal from petroleum ether solution.

The same procedure was employed by Mr. Takeuchi in 1953 and 1954 for the extraction of cannabis, in studies of the physiological activity under grants of the Agricultural Ministry.

In 1940, Remziye Hisar and Sazile Edesen reported their study of the absorption of the cannabis resin in petroleum ether solution by animal charcoal.

The method of extraction is shown below:



The amounts of extractables in each fraction, No. 1 to No. 4, separated by this procedure from 15 kg of cannabis plants, were as follows :

Fraction	Amount *Grammes*	Yield *Per cent*	Character
1	30.0	0.20	Brownish black, half solid
2	50.0	0.33	Yellowish brown, jellied with fine crystals
3	145.5	0.96	Dark reddish brown, viscous
4	28.5	0.19	Dark brown, viscous

Colour Reaction of Cannabis Extract

A number of colour reactions observed by various researchers with cannabis resin were examined. A few of these are :

(*a*) Beam's reaction (alcoholic potassium hydroxide);
(*b*) Ghamrawy's reaction (p-dimethylaminobenzaldehyde);
(*c*) Duquénois' reaction (vanillin, acetaldehyde);
(*d*) Diazo reaction (sulfanilic acid, sodium nitrite);
(*e*) Gibbs' reaction (2,6-dibromoquinone-4-chlorimide).

(a) *Beam's Reaction*

This reaction is the best-known for the identification of cannabis, and is characteristic of cannabidiol, which is physiologically inactive.

This component is absent from the extract of hemp plants grown in Japan that we tested, and no spot could be detected by the Beam reagent on filter paper in the chromatography of that extract.

Pure cannabidiol, however, gives a very distinct colour reaction, and can be easily detected on filter paper by this reagent, in the manner described in Duquénois' article.

Therefore, it is concluded that our domestic hemp at flowering contains no cannabidiol, or certainly very little.

It is pointed out in the literature that Beam's test on resins from some varieties of cannabis gave negative results.

(b) *Ghamrawy's Reaction*

(c) *Duquénois' Reaction*

(d) *Diazo Reaction*

These three reactions are also well known for the identification of hemp. All fractions of hemp extract that we examined gave positive reactions.

(e) *Gibbs' Reaction*

Phenols with no substituent in the para position to the hydroxyl produce this reaction. Todd employed this reaction in his chemical elucidation of cannabinol, cannabidiol, and tetrahydrocannabinol, and reported that it is positive with these compounds.

The hemp plants grown in Japan and all fractions of hemp extracts that we tested gave this reaction, and it was possible to detect the reactive spot from hemp extract which was chromatographed on filter paper, as described in detail elsewhere in this report.

Of the fractions of hemp extracts, No. 3 and No. 4 gave deeper colour tests than No. 1 or No. 2, both by a colour test on the extract or on the paper chromatogram.

It is concluded from the colour reactions that our domestic hemp contains the same chemically active component or components responsible for these tests as cannabis from the hemp of other countries.

Detection of Cannabis Components by Paper Chromatography

In 1954, Duquénois reported his microchromatographic study on the identification of cannabis using Beam's reagent as colour developing reagent and ammoniacal acetone as solvent.

As described above, there is no component found in the extract of Japanese hemp which is detectable by Beam's reagent, so we used Gibbs' reagent as the developing reagent in the chromatography.

In our experiments, ammoniacal acetone which Duquénois used gave a spot nearly at the top of solvent, and so was not very suitable. Many solvents were tried experimentally to find a suitable developing solvent, but they were all unsatisfactory in terms of shape of the spot, Rf value, and trailing, on an ordinary filter paper.

Then we used an alumina-impregnated filter paper. Of the solvents tried on this paper, 95% methanol gave fairly good results.

Paper Chromatography

Filter paper; Toyo Roshi No. 50, 2.5 × 40 cm, impregnated with alumina.

Impregnation of filter paper with alumina : Filter paper is dipped in 30% solution of aluminium sulfate at 60-65°C for three minutes and hung in ammoniacal vapour for one hour in an air-tight container. Then it is washed with running water for six hours, and air-dried.

Container for chromatography : Toyo Roshi Type C.

Procedure : A base line is drawn 5 cm from the lower edge of the filter paper, paralleling that edge. On the middle point of this line, the solution of extract of hemp to be chromatographed is spotted.

Developing solvent : 95% methanol.

Height of development : approximately 25 cm above the base-line.

Movement of solvent : ascending.

Spot developing reagent : Preliminary trials with a number of reagents giving colour reactions with cannabis led to the selection of Gibbs' reagent as the most sensitive. A few of these are given below.

(*a*) Gibb's Reagent

(i) 5% sodium acetate solution;

(ii) saturated alcoholic solution of 2,6-dibromoquinone-4-chlorimide.

The filter paper is sprayed with solution (i), then with solution (ii).

(*b*) Ghamrawy's Reagent

Two cc of 10% hydrochloric acid added to 100 cc of 3% alcoholic solution of p-dimethylaminobenzaldehyde. The filter paper is sprayed with this reagent and dried at 60°C.

(*c*) Saturated Ligroin Solution of Iodine

The Rf values and colorations thus far obtained by this procedure using Gibbs' reagent were as follows :

Sample	Rf value	Colouration by Gibbs' reagent
Fraction 1	0.62	blue
Fraction 2	0.62	blue
Fraction 3	0.61	blue
Fraction 4	0.63	blue
Cannabidiol	0.71	purple
Pyrahexyl (Abbott)	0.58	bluish violet

Pyrahexyl is a synthetic analogue of tetrahydrocannabinol, and its chemical name is l-hydroxy-3-n-hexyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran.

The minimum quantities detectable of the fractions No. 2, 3, and 4, by Gibbs' reagent in the chromatographic procedure

Table 1

Sample	Solvent	Max. (mμ)	Absorbance	Min. (mμ)	Absorbance	Concentration (g/l)
1. Petroleum ether extract	Alcohol	280	0.610	251	0.410	0.0520
2. Fraction 2	Hexane	—		—		0.0352
3. Fraction 3	Alcohol	282	0.559	251	0.178	0.0290
4. Fraction 3	Hexane	279	0.520	251	0.175	0.0283
5. Fraction 4	Methanol	281	0.332	253	0.176	0.0256
6. Pyrahexyl	Alcohol	276	0.741	249	0.224	0.0218
		229	1.700			
7. Pyrahexyl	Hexane	275	0.800	248	0.276	0.0239
		226	2.000			
8. Pyrahexyl	Methanol	275	0.742	248	0.245	0.0216
		228	1.750			

The absorbance value was transformed into extinction value $E\,\frac{1\%}{1\,cm.}$

Table 2

Sample	Solvent	Max. (mμ)	$E\,\frac{1\%}{1\,cm}$	Min. (mμ)	$E\,\frac{1\%}{1\,cm}$
1. Petroleum ether extract	Alcohol	280	117.5	251	78.8
2. Fraction 2	Hexane	—		—	
3. Fraction 3	Alcohol	282	192.9	251	61.4
4. Fraction 3	Hexane	279	183.6	251	61.8
5. Fraction 4	Methanol	281	129.8	253	68.8
6. Pyrahexyl	Alcohol	276	340.1	249	102.8
		229	780.3		
7. Pyrahexyl	Hexane	275	335.2	248	115.6
		226	838.0		
8. Pyrahexyl	Methanol	275	343.5	248	113.4
		228	810.3		

$E\,\frac{1\%}{1cm.}$ is plotted against wavelength. The curves are shown in Figs. 1 to 3.

were 600γ, 50γ, and 50γ, respectively. The spot of cannabidiol, the Rf value of which is 0.71, can also be developed by Beam's reagent. But the spots of the hemp extracts No. 1 to No. 4 were not shown by this reagent.

From this result and the Rf value, it is concluded that the spot of the extract of hemp grown in Japan detected by Gibbs' reagent on filter paper is produced by some other compound than cannabidiol.

Spectrophotometry of Cannabis Resin

The ultraviolet absorptions of cannabinol, cannabidiol, tetrahydro-cannabinol, and analogous compounds were measured by Adams and Todd in their studies of the chemical structure of cannabis components.

Biggs and Farmilo applied ultraviolet spectrophotometry of a petroleum ether extract to the identification of the cannabis plant.

It is also reported by Adams, by Todd, and by Farmilo that although some variations occur in the absorption curve of isomers of tetrahydrocannabinols, these compounds can be identified with good success by the measurements of ultraviolet spectrophotometry.

The ultraviolet absorptions of the extracts from our domestic hemp and of the synthetic analogous compound, pyrahexyl, at 216 mμ to 320 mμ in methanol, and in hexane, and at 220 mμ to 320 mμ in alcohol, were measured by the Beckman DU spectrophotometer for the petroleum ether extract, and by the Hitachi EPU-2 instrument for other measurements.

The absorbances measured at the maximum and minimum are listed in Table 1.

Fig. 1. — Absorption curves (in methanol) of I : pyrahexyl; II : fraction 4

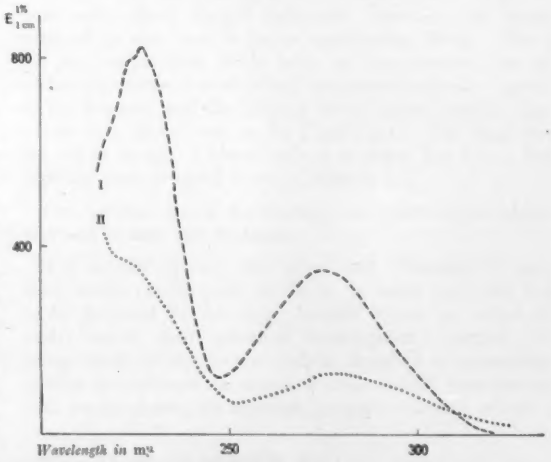


Fig. 2. — Absorption curves (in alcohol) of I : pyrahexyl; II : fraction 3; III : petroleum ether extract

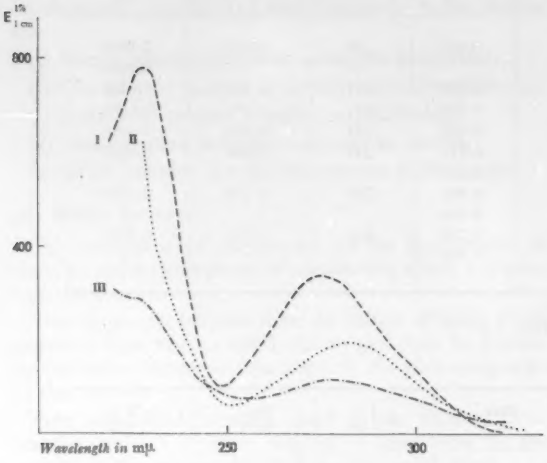
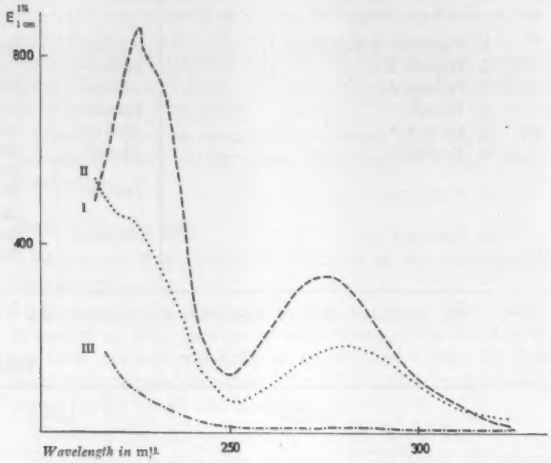


Fig. 3. — Absorption curves (in hexane) of I : pyrahexyl; II : fraction 3; III : fraction 2



The absorption curve shows there is no absorbing material in fraction 2. The spectra of fractions 3 and 4 have maxima at 279-282, minima at 251-253 mμ, and are nearly analogous to the spectrum of pyrahexyl.

A corresponding maximum for pyrahexyl is at 275-276 mμ and minimum is at 248-249 mμ. Pyrahexyl has another maximum at 226-229 mμ.

No variation of the absorption curve was observed in different solvents.

From the spectrophotometric studies of our domestic hemp, it is concluded that it contains tetrahydrocannabinol, or an analogous compound; and in general the hemp plants grown in Japan give a resin more similar to the Malayan resin reported by Biggs than to the Canadian resin.

Future Work

Research on the following items is planned for the future : (*a*) separation and purification of each fraction by means of column chromatography; (*b*) physiological activity of each fraction; and (*c*) comparison of cannabis from the hemp plants grown in Japan, with cannabis of other countries, as to the content of active resin.

Treatment of drug addiction. Experience in India

by Sir Ram Nath Chopra,
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General considerations

Although drug addiction existed in the past on a more extensive scale in India than in any other country in the world, with the possible exception of China, relatively little attention was paid to its scientific, medical and social characters. Two commissions were indeed appointed to go into the matter during the last decade of the past century; a royal commission was appointed in 1893 to enquire into the prevalence of the opium habit, and a commission to investigate the question of cannabis drugs was appointed by the Government of India in 1895. These commissions collected a vast amount of valuable general information regarding the prevalence and effects of these drug habits, but unfortunately the medical and scientific aspects were not considered. More than sixty years have elapsed since these commissions did their work. Considerable changes have occurred since then in the two chief drug habits, those which relate to opium and cannabis. New drug habits have come into being. In spite of this, a study of the literature shows that very little attention has been paid to the problem, except perhaps that which is described in the limited studies made by the senior author of the present article and his colleagues. There is hardly any other reference to the drug addiction problem in the medical literature of India during recent years.

The habitual use of stimulant, sedative and euphoric drugs was probably prevalent in India before it was in any of the other countries of the modern world. The "Soma" juice was a favourite drink of the ancient Aryan settlers, and was regularly taken by them centuries before the Christian era. What exactly the soma plant was is not known, though a number of plants, such as *Cannabis sativa*, *Ephedra vulgaris*, *Asclepias acida* have been mentioned. During the Hindu period — i.e., up to the eight or ninth century — alcoholic beverages were commonly used, as well as the preparations made from *Cannabis sativa*. These not only produced sedative effects, but also brought about euphoria in the form of pleasant dreams, forgetfulness, feeling of power, and also, it would appear from the writings of that period, voluptuous satisfaction. The opium poppy and the opium itself were introduced on the west coast about the ninth century with the arrival of the Mohammedan traders, and opiates soon came into use. Opium, on account of its strong effects, appears to have taken a great hold of the people, and the poppy began to be extensively cultivated all over the country. Opium was eaten, drunk or smoked by all classes of society. A most pernicious feature was that it was given to infants to keep them quiet while the mothers were away at work. The authors have reviewed the habitual use of opium and cannabis drugs in India and its relationship to the quasi-medical use of these drugs in the country in papers already published in the *Bulletin on Narcotics*.* In the present paper, the object is to describe the authors' experience in the treatment of these and other common drug habits in India.

Special Features of the Problem

The problem of drug addiction in India presented many features which differed widely from those met with in western countries. In India, the drugs were generally used in a crude form and were mostly eaten, though smoking of opium and cannabis drugs was quite common. Purified alkaloids of opium were rarely used for their euphoric effects.

Habitual use of cocaine started quite accidentally three-quarters of a century ago in Bihar State. In spite of severe restrictions imposed on the importation, possession and sale of this drug by the Government of India, the habit spread from Calcutta along two main railway routes to Uttar Pradesh, Delhi, the Punjab, and to the north-western frontier (now in Pakistan). From Bombay, it spread to other large towns in that state, such as Surat and Ahmadabad. This drug was almost invariably taken orally, generally wrapped in betel leaf. It was hardly ever taken by injection or as snuff. During the period between the first and second world wars, the habit spread extensively and became a menace.

Of the other drug habits, the chloral hydrate habit deserves particular attention. It started when the price of spirituous drinks rose on account of increased excise duty. Most of those who drank alcohol habitually, especially the lower strata of society, took it for its intoxicating effects. When the price of alcoholic drinks went up, the ingenious idea of adding a gramme or so of chloral hydrate to the drink occurred to the drinkers, and the habitual use of chloral hydrate thus started in a limited area in the Punjab state. The drug was also taken in tea. Chloral hydrate is cheap, but toxic; and fatalities have occurred from its habitual use.

The habitual use of barbiturates and other similar drugs was and is very rare in India.

It is worthy of note that drugs used habitually in India were mostly raw or crude products. In many cases, they had to be prepared by the addict himself before use, which in itself limited their excessive consumption. Further, by using crude products, the addicts absorbed comparatively smaller quantities of the active principles which were responsible for producing the euphoric, narcotic and toxic effects.

* Vol. VII, No. 3-4, and Vol. IX, No. 1.

A large number of addicts from the lower strata of society were so poor that they had not the means to carry the indulgence of even these crude and cheap drugs to excess; the upper classes were temperamentally more moderate. Besides, India is pre-eminently an agricultural country, which makes it possible for the majority of its inhabitants to lead a comparatively free and easy existence. The strain and stress of life which drive other people to the habitual use of sedative drugs is not very great.

In spite of all these factors, the problem of drug addiction assumed very great importance from its very extensiveness. The magnitude of the problem may be judged from the fact that, whereas in most of the countries in Europe and America the addiction rate of the population was from 0.1% to 0.2% or even less, in many states of India the rate was 1% to 3% or even more till recent years — i.e., the period between the two world wars. The drug habit was responsible for much economic loss, but also led to physical and mental deterioration of the habitués, thus making it a serious health problem.

Another noteworthy feature of drug addiction in India, especially in so far as opium and cannabis drugs are concerned, was the religious and social aspects of the problem. Indulgence in opium on account of age-long usage and custom was sometimes compulsory on such occasions as marriages, deaths and social gatherings among certain classes. Cannabis was considered to be the food of the gods by some, and was offered in temples on religious festivals and ceremonial occasions. Some religious sects took these drugs in the belief that they help the individual indulging in them to free his mind from worldly distractions, and in this way to concentrate on the deity. This is the reason why in places of religious worship, such as Benares, Mathura and Puri, there was enormous consumption of these drugs which still persists, though such use has decreased considerably during recent years (Chopra & Chopra, 1955 and 1957).

The medical and quasi-medical use of opium and cannabis drugs was also a very important factor. In a vast country such as India, where the facilities for medical relief were poor, the majority of the population did not get the benefit of western medical science. Sedative drugs such as opium and cannabis preparations were largely used as household remedies, and habits were often formed from such use. The doping of infants with opium could partly be attributed to this. It was firmly believed by the ignorant masses that opium was a wonderful tonic for children, stimulating growth and preventing sickness. The present writers have discussed fully the medical and quasi-medical uses of opium and cannabis and the large variety of conditions for which these were used as household remedies (Chopra & Chopra, 1955 and 1957). Almost all the diseases for the relief of which opium and cannabis drugs were used were of a minor character. Often the drugs were taken to dry secretions from the conjunctiva and the respiratory tract. Many people suffer from toxaemias of focal sepsis, which produce pains of rheumatic and neuralgic type, mental depression, irritability and hypersensitivity of the nervous system. These drugs in small doses gave relief, and this occasionally led to habitual use.

Opium was believed to allay fatigue and even stimulate physical energy. Those who had to manage coolies in tea-gardens and labourers in rice and wheat fields in India appreciated the value of these drugs to those who had been exposed to cold and chill. The present writers found that in former times the use of opium often increased during the harvest season in many districts in the Punjab by as much as 50%.

Drug Addiction and the Medical Profession

The medical profession in India was unfortunately not very well informed on the subject of drug habits and their treatment. During the course of their work in different parts of the country, the present writers came across few medical men with any considerable knowledge regarding the harmful effects of habitual use of drugs or of the phenomena which accompany abstinence when the drugs are withdrawn in order to rid addicts of the habit. The general impression appeared to be, "Once a drug addict, always a drug addict; he is incurable and that is the end of him." Ordinary hospitals generally refused to admit drug addicts for treatment. The few mental hospitals that existed were not suitable, for many reasons. There were no specialized institutions anywhere in India, and institutional treatment of addicts under expert guidance was unknown. It would certainly have been an advantage if some institutions of the type of abstinence sanatoria found in western countries had been established in areas where the incidence of drug addiction was high, so that treatment could be carried out on scientific lines. There is no doubt that the public would have taken advantage of these institutions. The present writers' experience, so far as the treatment of drug addiction is concerned, was therefore limited to the non-institutional method.

It is indeed fortunate that the importance of prophylactic measures as preventive of drug addiction has now been fully appreciated by the medical profession in India, and most habit-producing drugs are now used with great care. While an analysis of histories of drug addicts in western countries shows that the medical man has sometimes been unwittingly responsible in starting addiction, in India the present writers have not come across many cases in which addiction to opiates or cannabis drugs could be attributed to their use by medical practitioners in the first instance. With cocaine and morphine addiction, however, this has occurred quite frequently. In India, where addiction to crude drugs was in vogue and addiction to purified substances was uncommon, the prophylaxis by the doctor does not play such an important part as in western countries. The stringent restrictions imposed by the Government on the distribution and sale of narcotic drugs (opium and its derivatives, cocaine, etc.) has to some extent safeguarded the spread of addiction to purified substances. Such drugs are not allowed to be sold except when prescribed by a qualified medical practitioner; the dispensing chemist has to keep a careful account of every grain of the drug sold in books kept for the purpose, which are frequently examined by the excise authorities.

Type of Drug Addicts to be treated

From the point of view of treatment, the drug addicts in India can be divided into three main groups :

1. There is a large group which uses opium or cannabis drugs in small or very moderate quantities. The majority of these started the drug after middle age, generally for some minor disease or ailment. They usually started with a small dose and did not increase it. The narcotic and the euphoric effects of the drug have no attraction for them; indeed, these were not produced in this group at all. The habitués thus have

not the temptation to increase the dose, in fact they fully appreciate the evil effects which could result from such an increase. Most of them are good and successful citizens, and carry on their daily work quite efficiently. The present writers have known numerous persons who have taken small doses of opium (half a grain or so) or cannabis drugs for twenty to thirty years without any apparent harm, and have lived to a ripe old age. The use of the drug was started during the middle period of life for some minor ailment such as cough, looseness of the bowels, mild joint pains, etc., and it was found that it afforded relief. It appeared to do no apparent harm and was therefore taken daily. As a matter of fact it appeared that the drug was actually doing them good, as its discontinuance made them ill and prevented them from carrying on their ordinary work. It stands to reason that, when a person can lead an active and useful life on fixed and unchanging doses, there could hardly be any mental or moral deterioration. Treatment in this group, which was not insignificant in the old days, would appear to be quite unnecessary. Some of this group, however, gradually increased their doses and suffered from the effects of the drug. In such cases only was treatment desirable or necessary.

2. The next group — and a very large one — consisted of those who owed their entry into the paths of addiction entirely to association with and the example of other addicts. Some of these were normal individuals who were anxious to be treated, and they responded quite well to treatment. A proportion, however, started the habit from idle or deliberate seeking after new sensations. They took to the drug for its pleasure-giving effect and for sexual stimulation; these people were generally found in large towns. Many of them had some defect in their character and mental make-up, and appeared to be engrossed in furthering their indulgence and increasing the doses. They also had a tendency to indulge in more than one drug at the same time — e.g., alcohol and opium; alcohol and cocaine; alcohol, opium and cannabis drugs. This class of vicious addict was the most difficult from the point of view of treatment. Fortunately, this type, corresponding more to those met with in western countries, was not commonly met with in India. The few that existed belonged generally to the rich and indolent classes. They did not seek treatment, and nothing short of forced confinement in a special institution and prolonged training and reconstruction of character would restore them.

3. There was the third smaller group of habitués who had started using the drug in an attempt to tide over a period of special strain, overwork and fatigue. This class of addict was the product of large towns, and their percentage was not nearly so high in India as in the west. This was the class anxious to get rid of the habit; they were easily amenable to treatment, and did very well even under non-institutional treatment.

Treatment of drug addiction under Indian conditions: Different forms of treatment

It may be stated at the outset that the term "cure" used throughout this paper is in the limited sense of successful complete withdrawal of the drug of addiction. It was not possible for us to keep the treated addicts under observation for sufficiently long periods to be sure that a radical cure had been effected and the habit permanently eradicated. Besides this, we had no facilities to carry out the after-treatment, which is absolutely essential, following the withdrawal of the drug. Nor was it possible for us to give them rehabilitation treatment which is an essential factor in the production of complete cure. This was the case in the small preliminary series of 200 addicts who were treated in the Carmichael Hospital for Tropical Diseases, and more so in the case of the mass treatment which was carried out in Assam.

Sudden and Gradual Withdrawals

The withdrawal of the drug by the "sudden" method advocated by Bonhoeffer has been recognized to be scientifically the best method of treatment in some countries. In spite of the success achieved with it in Europe and America in special institutions for the purpose, it has not been possible to carry it out in India. We have tried the method, but have met with little success. The reason is that the conditions under which the addicts were treated were far from ideal. There are no specially equipped institutions in India where addicts undergoing this form of treatment can be housed and can have all the facilities to help them through the critical period of withdrawal. The post-withdrawal insomnia and the digestive and other troubles have been extremely distressing and have needed careful and efficient handling. Some of our patients had to be treated in the wards of an ordinary hospital. Some were treated in their own homes, where the success of such treatment was doubtful from the beginning. Our experience, therefore, with regard to the "sudden withdrawal" method is limited and unsatisfactory from every point of view. Although we have no personal experience of such treatment in specialized institutions, we have no hesitation in saying that, as far as Indian addicts are concerned, the sudden withdrawal under existing conditions would imply a period of frightful physical and mental suffering which the majority of them would be unable to bear. The shock of sudden withdrawal would be too much for many of the addicts, and even those with strong will-power, determined to get rid of the habit, could stand it only with difficulty. It would make the most willing and determined of them lose confidence, and they would end by refusing to go through with the treatment. Their suffering would make them lose their faith in the treating physician, and they would become distrustful and hostile, so that it would become difficult to establish friendly relations or to inspire confidence in them. We have often heard inveterate opium eaters remark that they would rather endure hell than the abstinence syndrome. Experience in India is in accord with that of many authorities in the west who consider that the patients subjected to harsher methods of treatment, such as locking them up and letting them "suffer it out" are the very ones that are more likely to relapse and go back to the habit.

These remarks apply to the opium addicts only. In the case of cannabis drugs, cocaine, chloral hydrate, etc., sudden withdrawal can be carried out under non-institutional conditions, in the case of Indian addicts, without any great difficulty.

In opium addicts, we have met with a great deal of success with the *slow or gradual withdrawal method*. There is no doubt

that whether the process of withdrawal is gradual or sudden, a great deal of suffering has to be undergone by the addict. Administration of other drugs in any amounts will not completely eliminate the distressing withdrawal syndrome. With the gradual method, however, the pain and discomfort of actual withdrawal are reduced to the minimum. If due attention is paid to the psychological side of the treatment and the patient is assured that the physician thoroughly understands his trouble and is doing his best to relieve him of his sufferings, the chances of a permanent cure are greatly enhanced. The patient may even carry not very unpleasant memories of his restoration period. Another advantage is that the post-withdrawal insomnia, which is an extremely distressing condition, is much less frequent. Moreover, under conditions existing in India, it appears to be the method of choice. If the withdrawal is effected with reasonable celerity and with as little discomfort to the patient as possible, it will encourage other addicts to seek the treatment, and those who have relapsed may also return.

While it cannot be said how long it would take an Indian patient to be cured, if he were to undergo treatment in a properly equipped institution by the sudden withdrawal method, the experience of many European institutions is that at least a three months' stay is necessary. The adoption of such treatment would therefore be very expensive for a country such as India. Our experience is that with the slow withdrawal method it takes three to six weeks to effect a cure in most of the Indian addicts who are going to be cured. The decrease in dosage is carried out very gradually at first, so that it is imperceptible. After a few days it can be effected more rapidly, especially if some pill such as that containing nux vomica, gentian and black pepper is given as a substitute. The substitution is started with the morning dose at first, leaving the evening dose untouched; this procedure prevents insomnia. Minor symptoms such as diarrhoea, epigastric pain and nausea may be controlled by giving ordinary alkaline mixtures. Usually in three to four weeks the drug can be entirely stopped.

It cannot be denied that in spite of all precautions there are a large number of failures. In many cases when it appeared that all was going well, it was suddenly discovered that the patient was secretly obtaining a supply of the drug. The ingenuity shown by the addicts in this connexion, and the extraordinary way in which they evade those on guard, are amazing. The chances of the treatment's being prematurely suspended are also great. Even by the slow method the withdrawal cannot be effected except by exercising a great deal of compulsion. Most of the patients start with good resolutions but give way on about the second or third day when the symptoms are very acute and at their peak. To keep control over such patients under ordinary hospital or home conditions is very difficult indeed. With full knowledge of all these difficulties the gradual method was tried under non-institutional conditions with a fair degree of success, especially in addictions of short duration. Considerable care and attention had to be exercised in the selection of cases. Before starting the treatment the patient had to be thoroughly examined and any physical conditions which may have led to addiction — e.g., septic foci, etc. — had to be treated. Duration of addiction is an important factor; cases under five to seven years taking ten to fifteen grains daily were generally amenable to treatment. In many persons taking over twenty grains daily for prolonged periods, circulatory disturbances leading to collapse are likely to supervene if the drug is suddenly withdrawn. Sudden withdrawal is successful and can be recommended only with addicts taking under five grains daily.

The gradual withdrawal method is also suitable for mass treatment of opium addicts under non-hospital conditions. One of us during the First World War in the East African campaign was attached to a company of Sikhs about 200 strong. Most of them were heavily addicted to opium, some taking as much as 100 grains daily and some even more. With the co-operation of the officers of the company there was no difficulty in cutting down the dose to a few grains a day in a couple of months, without any of the men showing any signs of distress. They gladly went through the cure, and some of them gave up the habit entirely. As there were no towns near by, the chances of anyone's obtaining local supplies were completely eliminated.

Chopra (1937) has shown that there is a certain amount of psychic element in opium addiction and the production of withdrawal symptoms. He has come across cases of persons addicted to large doses of opium (20 to 100 grains a day) who had been sent to gaol for some criminal offence and whose supply was inevitably stopped; they did not, however, suffer from such marked abstinence symptoms as some of the others. During the treatment of addicts to rid them of the opium habit, the drug can largely or totally be replaced by substances such as gentian and nux vomica in pill form without the patients realizing it. An interesting observation is that if the patient is not aware that he is taking opium, the drug can be effectively given for weeks or even months for its therapeutic effects, without producing addiction or abstinence symptoms. A great deal can be done by obtaining the co-operation of the patient. Proper attention to the psychological side of the treatment ensures success in many cases.

Administration of Opium to Infants

The habit in infants and children is not difficult to break. In the usual course of events, the parents continue to give opium up to the age of two or three years and then, when the child can take care of itself, the drug is stopped. Both the gradual and sudden methods of withdrawal were tried with an equal degree of success, but it is better to adopt the sudden method. The psychological element plays a very minor part in children, and as a rule there is little discomfort. The withdrawal symptoms met with are looseness of bowels, diarrhoea, and loss of appetite. Nausea and abdominal pains also occur. Diarrhoea can easily be controlled by powders containing sodium bicarbonate, bismuth carbonate and aromatic chalk. In severe cases with mental irritability, a bromide mixture with a few minims of tincture of belladonna may help to relieve symptoms. The child is quite well in a few days, and a cure is effected; as a rule, no after-treatment is necessary. Even in the worst cases, with marasmus and emaciation, the patients begin to put on weight soon after they are rid of the habit.

Opium Smoking

The experience in India is that the habit of opium smoking is much more difficult to eradicate than opium eating. Fortunately, owing to enforcement of very strict regulations, the habit of smoking opium has practically disappeared. There appears to be little doubt that an opium smoker is much

more attached to the drug than an opium eater. It would appear that, although smaller quantities of the alkaloids are absorbed (most of them must be destroyed by the heat produced), the absorption is very rapid through the large surface of the capillaries of the lungs, and the effects are sudden and more intense, resembling those of an injection of morphine. The treatment of opium smoking has not been properly worked out in India. Some authorities allow the patient to take the drug by mouth and gradually cut down smoking. Once eating is successfully substituted for smoking, the addict becomes more amenable to treatment.

"Post" (Unlanced Capsules of P. somniferum*)*

It is a common belief among the addicts that "post" does less harm than opium. Our experience in this respect, however, is not in accord with this view. A person addicted to poppy heads requires comparatively much larger doses of opium to produce a similar effect; moreover, the physical and mental effects produced by ordinary doses of "post" are much more marked than with moderate doses of opium. This in all probability is due to the potentiating effects that the constituent alkaloids of poppy capsules have on one another. It is more difficult to get rid of the habit of taking "post" than the habit of taking opium. The sudden withdrawal method is rarely practicable in these cases, the gradual method being the only one which meets with success. The dose is gradually reduced by half a capsule till a fourth of the original dose is reached, after which the drug is stopped altogether.

Cannabis Drugs

The treatment of the cannabis drug habit is not so difficult, though here again, as in the case of opium, it is easier to cure the eating habit than the smoking habit. Withdrawal symptoms, as they are met with in the case of opium addicts, are hardly ever seen in the case of cannabis drugs — indeed, the patients find no difficulty in giving up the habit of their own accord if they wish. In northern India, many people indulge in bhang drinking in the hot weather, on account of its reputed cooling and refreshing properties, and give it up in the winter quite suddenly without any discomfort. Cannabis preparations, when taken habitually by mouth, can be suddenly withdrawn without producing any marked abstinence symptoms, though keen desire to indulge in the drug is there. Temporary loss of appetite, constipation lasting for a few days and rarely palpitations and restlessness may occur; all these can easily be dealt with.

Charas and ganja are stronger preparations and, as these are generally indulged in by smoking, their effects on the system and particularly on the nervous system are more pronounced. The will-power of the smoker is weakened, and without the physician's help he is not able to give up the habit. Treatment in special institutions with facilities for forcible withdrawal is likely to give the best results. The psychological and mental treatment, and training and education of the addict are as important in the case of cannabis smokers as in opium addicts, in spite of the fact that the physical distress accompanying withdrawal is largely absent.

Cocaine

The habit of eating cocaine is easier to cure than that of cocaine injected parenterally. Removal of the addict from the environment in which he has acquired the habit and from associates in whose company he indulges in the drug, preferably to a place where he cannot get it, often effects a cure. The present writers know of many instances where individuals from one part of the country went for months to another part where they were unable to get the drug and where they had no associates; they were able to conquer the craving for many months at a time without difficulty or any marked distress. When, however, they returned to their old surroundings and associates they again succumbed to the temptation. Similar facts have been observed in addicts who have been confined in prisons. They also give up the habit during confinement and go for years without the drug, but they generally take it up again after discharge. We are convinced that cocaine eating is comparatively a much milder form of indulgence than cocaine administered by the parenteral route.

Psychotherapy and mental training are important; the psychological rearrangement of the personality by finding some innocent emotional compensation will often help the addict to give up the habit. The drug must be withdrawn all at once and symptomatic treatment given for the withdrawal symptoms. In our experience in India, the cocaine habit, next to the opium habit, is perhaps the most difficult one to eradicate.

Auxiliary Treatments

Atropine and hyoscine have been tried in the earlier stages of withdrawal of opium, and strychnine in the later stages, with good results. The belladonna hyoscyamus mixture recommended by Lambert is useful in that it lessens the shock, decreases diarrhoea and relieves insomnia. Gastrogenous phenomena are not so marked in the treatment of the opium habit as with morphine, and alkaline and acid treatments are not necessary. Adrenaline and ephedrine have been tried for mitigating the withdrawal symptoms in a few cases, with good results. It is rarely necessary in this country to use sedative drugs, such as codeine, narcosan, luminal, sodium amytal, pernocton, etc., in the g dual withdrawal treatment of opium eaters, and we have had little experience in the use of these drugs.

Insulin Treatment

Insulin either alone or in combination with glucose has also been tried in Europe. Sakel (1930) used insulin alone in doses up to 80 units in 24 hours to combat the withdrawal symptoms in cases where morphine was cut off abruptly, with satisfactory results. Braun administered bigger doses of insulin, and in addition employed soporifics such as luminal. We have tried this method with little success.

So far as opium eating is concerned, we have tested the effects of the drug on the blood sugar of both diabetic and normal Indian patients. Small and moderate doses of opium have little or no effect on the blood sugar of individuals who are not suffering from disturbances of carbohydrate metabolism. In case of persons whose blood-sugar content is abnormally low, opium may raise it. The blood sugar in the early and mild types of diabetes may be actually reduced. It is only in the severe forms of the disease that the blood sugar is actually raised. In some patients, opium does no more than raise the renal threshold of sugar excretion. Our findings with regard to opium agree with those of Simenauer & Pulfer and Anton, who found that in human beings, as opposed to

animals, morphine produces little or no disturbances of the carbohydrate metabolism.

Diuretics

The usefulness of diuretics such as novasurol or euphyllin in the slow withdrawal method is doubtful. Our observations show that in addicts taking moderate and large doses of opium there is retention of fluid in the blood. In those taking small doses, however, the output of urine is actually increased, and the blood is not altered. When the kidneys are damaged and there is albuminaria, the administration of one to nine grains of opium daily produces an appreciable decrease in the quantity of urine passed. In none of the cases was there indications of added damage to the kidneys, which the drug is reputed to cause in such cases.

Vesicatory Serum Therapy of Modinos in Opium Addiction

This method is very simple. A cantharides cerate plaster to a size of 8 cm^2 is applied to the patient's chest or abdomen, and after ten hours serum varying from 2 to 8 cc. is taken from the resulting vesicles and re-injected into the upper part of the arm or leg. The operation is repeated on the third or fourth day, and a third injection is given four to six days after the second. The dose of the narcotic drug is rapidly reduced, and may be completely cut off within three to seven days. It is believed that antibodies are formed which create a distaste for the drug, but this view is not universally accepted, and this distaste is attributed by some to the production of hypersensitivity. Other authorities hold that the so-called hypersensitivity is not specific, but is merely psychological and may be obtained by injecting common salt solution. It is further stated that relapses after the treatment are as common as with other methods.

Our experience with this form of treatment is limited, but the method was tried in the treatment of opium addicts in Burmese gaols. Opinions among the medical officers trying the treatment were unanimous on one point — namely, that one or more injections of the autoserum from a blister make the addict sensitive to opium. The patients say they do not wish to take opium any more, not because they do not like it, but because the consumption of the drug even in small quantities did not produce the pleasure or exhilaration that it used to produce before. On the contrary, headaches, nausea, vomiting, etc., were produced. A distaste for the drug is thus developed, and since the euphoric effects are not produced, opium is not wanted. A control experiment was also tried in the following manner. Some addicts were blistered in the usual way and the fluid from the blister was injected; in a number of other addicts injections of normal saline were substituted. It was found that the addicts who had normal saline did not respond in the same way as those in whom actual serum was injected. In other words, mere blistering did not do any good so long as the serum was not reabsorbed; nor were the effects due merely to the psychological effects of the injection. It is difficult to say how long the sensitiveness to the drug of addiction will last, if it is produced. It must be remembered, however, that most of the addicts were prisoners under prison discipline and living under conditions in which temptations by way of easy access to opium did not exist. In one of the jails, the treatment was tried on two warders who were free to go about and could easily obtain opium if they so desired. In both cases, the injections of serum produced the same effects as in the prisoners.

Whether the treatment will eventually produce a permanent cure or not is difficult to say with any degree of certainty, but the results so far obtained are certainly striking in some cases. The patients got rid of the habit and gained weight after the treatment; appetite returned and general health improved in a remarkable manner. The following provisional conclusions can be drawn from the few data obtained:

1. That the treatment with vesicatory serum injections is a valuable measure in the treatment of opium addicts.

2. That the addicts who have any will-power left will probably be completely and permanently cured of the habit through its agency.

3. That those who have no will-power left, although they may be temporarily benefited, will probably relapse as soon as they have the opportunity.

Lecithin Treatment

The lecitin treatment of opium addicts was suggested by Ma Wen-Chao (1932) and was tried in India by us. From certain observations made on the physical properties of the blood sera of opium addicts, it was found that the protein content, specially the neuro-protein content, was lacking or deficient, particularly during the withdrawal period. Ma Wen-Chao (1932), from a cytopathological study of chronic morphinism in albino rats, found that the withdrawal of the drug in the addicted animals led to severe pathological conditions of the Golgi apparatus in the cells of various organs. Without treatment these conditions are overcome in ten to twelve days. Feeding with lecithin, on the other hand, for a period of six days before and for some days after prevented the Golgi apparatus from becoming abnormally reduced; this was accompanied by a condition of general well-being of the animals, which was absent in those receiving no lecithin. The treatment with lecithin was tried successfully in China on 143 opium smokers. In addition to their ordinary diet, the patients were given six to nine eggs daily to enrich the diet in lecithin. The bouts of craving were overcome by administration of tincture of opium in small doses. The lecithin given was prepared from eggs and made into pills with glycyrrhiza powder. The usual daily dose given was four to six grains. It was found in most of the addicts that although lecithin prevented many of the untoward symptoms, it was insufficient to combat all the withdrawal symptoms by itself.

Our preliminary trials with lecithin treatment of opium addicts in India were so successful that we decided to give it an extensive trial in cases under close observation in the Hospital for Tropical Diseases, Calcutta, and, if possible, to improve the technique of treatment. Intensive studies were undertaken in the first instance to determine the changes produced in the body by prolonged use of opium, which gave rise to such intense and unbearable abstinence symptoms. It was thought that these studies might give a clue as to how such symptoms could be combated. The result of these investigations was published in a series of papers.

Treatment with Lecithin and Glucose

In view of the biochemical and biophysical findings briefly described hereafter, a modification of the Ma Wen-Chao method of treatment of opium addiction was evolved and tried in a series of 200 addicts in the Hospital for Tropical Diseases, Calcutta. Briefly, the method is as follows:

On the evening before treatment was started, the patient was given a dose of two to three grains of calomel, followed by saline purgative the next morning. The drug was then suddenly and completely withdrawn, and the addict was watched for the development of withdrawal symptoms, which in the majority of cases started to appear on the same day and attained their maximum within twenty-four hours. The actual treatment was at first started when withdrawal symptoms became intense and unbearable, in order to study the biophysical and biochemical changes which are produced in the individual during this period. Later, it was found distinctly advantageous to start administration of lecithin and glucose the day before opium was withdrawn, so that the inconvenience to the patient was reduced to the minimum.

Lecithin (Ovo lecithin, Merck) was given orally in the form of pills containing five to twenty grains three times a day, and continued usually for five consecutive days. In a number of patients, lecithin administered by mouth caused nausea, and in such cases the drug was given by injection in the form of a colloidal solution, twice daily. Experience showed that lecithin, when given by injection, acted more effectively and better than when it was given by mouth. Besides this, the amount required to produce the desired effect was comparatively small, and consequently the cost of treatment was considerably reduced. During this period of abstinence, the patient was encouraged to take plenty of fluids and glucose by mouth, as these greatly ameliorated the withdrawal symptoms.

There is no doubt that in the majority of cases lecithin decreased the intensity of the withdrawal symptoms and shortened their duration. In spite of its administration, the abstinence symptoms were severe in some addicts, and in such cases intravenous injections of 20 ml of 25% glucose solution, as well as glucose administered orally, greatly helped to ameliorate the condition. These were given with a view to stocking the liver with glycogen, and in order to enable it to cope with the strain, which undoubtedly fell on this organ, during the process of elimination of morphine and other alkaloids of opium from the system. We usually gave an intravenous injection of glucose every morning for the first three or four days, and if necessary repeated it in the evening, when the symptoms were severe. The injections were then stopped, and oral administration of glucose was repeated if needed. In severe cases attended by cramps, an addition of 10 ml of a 10% solution of calcium gluconate to the glucose solution helped greatly. No other drug was necessary during this period except a brisk saline purgative every morning, to help in the elimination of the drug through the gastro-intestinal tract. As a rule, no further treatment was required after the first week.

The diet during this period was kept light because addicts as a rule could not take much, on account of the gastro-intestinal disturbances produced by the withdrawal. Glucose, milk and fruit juices were given freely by mouth for the first two or three days during the withdrawal period. On the fourth day, when the abstinence symptoms began to disappear and the appetite returned, a diet rich in proteins and lecithin in the form of eggs, milk, beans, fish, chicken, fruits, bread and butter was given.

After the completion of the actual treatment — that is, after the complete withdrawal of the drug was effected — the patients were kept under observation in the hospital for a fortnight or more. A twenty-four hour specimen of urine was examined for the presence of opium alkaloids, in order to see if any of the patients were taking the drug secretly Usually the alkaloids can be detected in the urine for four to five days after the withdrawal of opium; after that, they cannot be detected, except in rare cases where excretion is prolonged. If, therefore, the alkaloids were still found after this period, the presumption was that the patient was indulging in the drug. If repeated examinations of the urine showed the absence of alkaloids, it was concluded that the drug was no longer being taken, and the addict was probably cured of the habit.

On the second day of actual treatment, most of the patients reported that the discomfort was decreased by half. When seen a few weeks after the treatment, many reported that the drug had lost its taste and charm for them, and in some, very small quantities of it even produced a sensation of nausea. The treatment undoubtedly gave rise, in a number of cases, to a definite feeling of aversion to the drug, whether by smoking or eating, and craving for the drug was definitely stopped in many cases.

In order to effect a permanent cure, a complete overhaul of every patient should be carried out with a view to determining if any septic or toxic foci are present in the body, as morbid conditions of this kind are a common distributing cause of opium addiction in this country. If routine laboratory examinations revealed such conditions as dysentery, sprue, helminthiasis, sinusitis, conjunctivitis, etc., these were treated during the period of observation after treatment.

The mental outlook of treated addicts also showed a remarkable change. After the treatment, persons who were previously sad, morose and apathetic and who had pale and sallow complexions, became cheerful, and their appetite and general health improved and they put on weight. They also became more sociable, docile and respectful, and showed an inclination to do their ordinary work. They felt interested in their surroundings and became definitely more active. After discharge from the hospital, it was ascertained that most of them had become useful members of society and followed their vocations with interest.

The total course of treatment varied from seven to twelve days, and during this period the change in the conditions of the addicts was remarkable. The patients treated in the hospital were kept under further observation for a period varying from four to twelve weeks in order to rehabilitate and train them for their new environment, and to watch for the occurrence of relapse. The period of rehabilitation and rebuilding of the personality of an addict may sometimes extend to a few months.

In this special series of 200 cases treated in the Hospital for Tropical Diseases (Calcutta) by this method, complete cure was effected in 70%, the dose was reduced by 80% in 10%, and by 50% in 15% of the cases. The treatment failed completely in 5%, and there was a relapse to the habit in the remaining 5%. Thus, it appeared that the results were more encouraging than with any other forms of treatment which had so far been tried in this country.

Rationale of Treatment with Lecithin and Glucose

Observations made by such workers as Maguin (1909), Sollier (1910) and Pierce & Plant (1928) have shown that in addiction of long duration, general dehydration of the body takes place owing to excessive perspiration, abnormal salivation and obstinate diarrhoea. These facts strongly suggested

that such a process of dehydration may have an ultimate effect on the fluid content of the blood. The changes in the physico-chemical properties or in the protein fraction of the blood in the addicts under treatment were determined. Chopra & Chopra (1935, 1937) found that in most of the addicts the state of addiction was invariably accompanied by an increase in the fluid content of the blood, and were inclined to believe that an excessive secretion on withdrawal would have a reverse effect, leading to an increase in the percentage of serum proteins.

The work of Chopra & Roy (1937) on the blood-lipoid changes in opium addicts before, during and after withdrawal pointed to the probability of a diminution in the water content of the blood on withdrawal, which led Chopra & Ganguly (1939) actually to determine the effect of withdrawal on the blood fluid, and also to attempt to explain the rationale of the treatment of opium addiction with lecithin and glucose. Blood sera from the addicts under treatment were examined for total proteins before, during and after the withdrawal of the drug. In most of the cases, it was found that concentration of proteins present in the serum before treatment underwent a definite increase during the withdrawal period and returned gradually almost to the pre-withdrawal value after the addict had undergone the prescribed treatment. The increase in the total protein content during the period of withdrawal, as a general rule, ran parallel to the appearance of withdrawal symptoms. Excessive outflow of water from the body caused the most marked withdrawal symptoms that have been observed in almost all the cases studied by us. This apparently points to a disturbance in the fluid equilibrium in general. The effect of treatment may therefore be taken to have restored the fluid equilibrium of the system to its previous level.

Chopra, Mukherjee & Chopra (1935) observed that increase of the euglobulin fraction in the serum of addicts probably meant an ultimate drainage of phosphate from the nerve cells. Lecithin treatment was, therefore, rational on that basis inasmuch as it would help to make up the deficiency. In the majority of cases, lecithin decreased the intensity of withdrawal symptoms ans shortened their duration. But in spite of its administration, the abstinence symptoms were very severe in some of the subjects, and in these, intravenous injections of 25 ml of 25% glucose solution helped to ameliorate the condition. Although lecithin by itself was unable to cope with the severity of the withdrawal symptoms, it doubtless removed the craving for the drug in the majority of cases.

The role of glucose in coping with the abstinence symptoms can thus be understood. By this treatment, the ultimate effect seems to be the restoration of the water balance. Therefore, any drug that confers a fluid-retaining power to the blood would be expected to have good effect. Carbohydrates in general and glucose in particular are known to possess this water-retention capacity. Glucose, therefore, in addition to stocking the liver with glycogen to enable it to cope with the unusual strain on this organ during the process of elimination of morphine, etc., helps the retention of water in the blood, and keeps up the blood hydration level to its normal value. From the above consideration, it may be concluded that lecithin tones up the nerves of the addicts by supplying the lipophosphates, and glucose helps to restore the disturbed water balance. It is, therefore, not difficult to see how these two together produce the desired effect in removing the drug craving and alleviating abstinence symptoms in opium addicts.

Abstinence Symptoms

We have already stated that in order to work out the rationale of the treatment, the addicts under treatment in hospital were allowed to develop the withdrawal symptoms in full before starting the actual treatment. The most common symptoms recorded during this period among the opium addicts were as follows.

Quite a number of patients suffered from cramps which were sometimes severe, epigastric pain, sinking sensation in the chest, insomnia, diarrhoea, vomiting, headache, asthenia, and inability to stand up and walk. A few patients taking large doses for prolonged periods developed feeble pulse, profuse perspiration, vomiting and severe diarrhoea, resulting in collapse. Spermatorrhoea and headache were also common. Hiccough was observed in a few cases.

Vasomotor disturbances such as sneezing, coughing and running from the nose and eyes were also commonly seen. Palpitation and cardiac distress were also observed in a few cases. Anorexia was a common symptom, and usually there was no appetite for the first three or four days and all food was refused. Over 50% of the patients suffered from insomnia, which was often very troublesome. It was observed that there was some psychical element in all these symptoms, and the addict could control the intensity of the withdrawal symptoms to some extent if he had a strong enough will-power to do so. Most of the addicts, however, especially those who were taking large doses, had lost their will-power entirely and were helpless.

Symptomatic Treatment

The following is a brief summary of the symptoms and complications which were observed and controlled in the course of treatment of this series of 200 cases in the hospital.

(i). *Pains in the body and limbs, cramps and general malaise.* The first two were very troublesome and often did not yield to ordinary analgesics; cramps were commonly met with, but they were not very severe. Simple measures such as massage, hot baths, aspirin and veramon were successful in some cases, but when the pain was severe an intramuscular injection of novalgin (Bayer) 2 ml. often proved effective. Hyoscine hydrobromide in 1/200 grain doses was also tried but was not found to be effective. The pains and cramps generally disappeared in three to four days after the administration of lecithin and glucose.

(ii). *Nausea and vomiting* were common symptoms, and were observed in 40% of this series. In twenty addicts there was actual vomiting, and in two it was very severe and incessant. Sucking of ice greatly relieved these symptoms, and in severe cases 10 drops of adrenaline hydrochloride (1 in 1,000 in normal saline) under the tongue every two to four hours often gave relief.

In two patients, severe bilious vomiting occurred, and the stomach had to be washed out with a solution of sodium bicarbonate (one drachm to a pint of water), after which the patients were relieved.

(iii). *Constipation* was treated with administration of saline every morning and, if necessary, calomel in half-grain doses was given the previous night. Diarrhoea was also frequently met with, and for this condition no special treatment was

given except fluid diet and withholding the daily dose of saline. In severe cases, bismuth and chalk mixture was given.

(iv). *Cardiovascular manifestations.* These were feeble and irregular pulse, sinking sensations, cardiac embarrassment and collapse. These symptoms were greatly relieved by administration of glucose by the intravenous route and cardiac tonics such as brandy, cardiazol, digifortis, etc., were effective. Special treatment for heart conditions had to be resorted to in ten cases. They were all aged persons who had been taking the drug for over twenty years and in doses above 40 grains a day, who showed severe reactions during the period of abstinence. In one patient, an old man, aged sixty-five years, who had been taking the drug in doses of 45 grains for a period of forty years, collapse occurred on the fourth day of withdrawal owing to excessive loss of fluid, due to persistent bilious vomiting and diarrhoea. The treatment adopted was intravenous administration of four to five pints of glucose saline, cardiazol and atropine sulphate injections and brandy by mouth. No opium was given. This patient was discharged from the hospital as apparently cured after twenty-one days.

(v). *Vasomotor disturbances* such as sneezing, coughing and running from the nose and eyes. Unless severe these require little or no treatment but, when troublesome, a small dose of Dover's powder (5 grains) at bedtime gave relief.

(vi). *Spermatorrhoea* was treated by a simple mixture containing 10 grains each of potassium bromide and ammonium bromide and 30 minims of tincture of valerian, administered twice daily; it allayed restlessness and induced sleep. This mixture was allowed to be taken after the patient was discharged from the hospital in cases where there were signs of restlessness and irritability.

(vii). *Insomnia.* This was a very troublesome symptom and was often difficult to treat. It generally started early in the course of treatment and sometimes continued for weeks. Often no treatment was given for this condition for a day or two, the patient being instructed to exercise his own will-power and try to sleep. Sometimes he was helped by such simple measures as a hot foot bath before retiring, or a dose of a mixture containing bromides at bedtime. When these measures failed, a pill containing 7½ grains of medinal administered at bedtime often succeeded in producing sleep for four to six hours. This produced a real change in the patient's mental condition and attitudes as he began to feel rested and gained confidence in the efficacy of the treatment. This drug should not be repeated for more than four successive nights. Other barbiturates and hypnotics, such as adaline, evipan, luminal, ortal (Parke, Davis & Co.) were tried with good results. In one serious case with intractable insomnia where nothing succeeded, 30 minims of tincture of *Rauvolfia serpentina* succeeded in producing sleep.

(viii). *General asthenia and loss of appetite.* For anorexia, which was a common symptom during the first week or so, a mixture containing gentian, alkalies and nux vomica before food was useful. The general lassitude and weakness following withdrawal were relieved by a simple mixture containing iron, strychnine and arsenic, which was usually prescribed to be continued for a few weeks after discharge from the hospital.

After-treatment

The importance of the psychological aspects of treatment of drug addicts has already been stressed. The responsibility of the physician does not end after the drug is withdrawn. The period following the withdrawal is most critical, and unless great care is taken relapses may occur. The whole of the nervous system has been strained and a thorough reconstruction and rehabilitation of the personality and the character of the addict are imperative if a permanent cure is to be obtained. The physician can do much by way of encouraging the patient and making him believe that by his will-power and firmness he will get rid of the habit. A common belief among Indian addicts is that elimination of the drug habit will leave them sexually impotent. There is no basis for such a belief, and the patient should be fully assured that loss of sexual desire, which they observe after giving up the drug, is a temporary phenomenon and is a part of the general loss of tone of the organs. It usually passes off in four to eight weeks, and sometimes it may last for several months. During the period following withdrawal, a good tonic in the form of vitamins, iron, arsenic and strychnine is helpful. Occupational therapy is also very important. As soon as possible, the patient should start doing some work so that his attention is diverted in other directions. He must lead a quiet life and avoid excesses of all kinds for a year or more after withdrawal has been successfully effected.

Results of treatment with lecithin and glucose: Mass scale trials

Chopra & Chopra (1949) were fortunate to try out the efficacy of this treatment on a mass scale in Assam during the anti-opium campaign of the first Congress Government in 1938. As early as 1925, the Assam Provincial Congress Committee, appreciating the demoralizing effects of the opium habit and its extensive prevalence among the population, appointed an inquiry committee to study the problem in detail (Assam Congress Inquiry Committee's report on the opium habit, 1925). The available data and suggestions embodied in this report are an excellent work of reference. In 1938, when the first Congress Government came into power, these recommendations were immediately put into practice.

After the necessary legislative measures had been adopted the state government decided to stop the sale and use of opium completely and immediately in the three upper and worst affected districts as an experimental measure, in spite of the fact that the prohibition meant a considerable loss of revenue to the already poor and undeveloped State of Assam. In April 1938, our colleague, Dr. G. S. Chopra, was deputed to assist the Government of Assam in conducting the great experiment of prohibition of opium. Previous to starting the campaign, vigorous propaganda was carried out through the local congress committees, missionary societies and other educational institutions all over the state. Public meetings were organized, and pamphlets and leaflets describing the harmful effects of the opium habit were distributed freely. The evils of the habit and the necessity for its eradication, together with the effectiveness of the treatment which the addicts were to undergo, were fully explained. This helped

greatly in preparing the ground for a mass campaign of treatment which would lead ultimately to the rooting out of habitual use of opium.

Census of Addicts

Before actually starting the campaign, a census of both the registered and unregistered addicts was carried out with the help of the local excise and police personnel. The unregistered addicts — i.e., those who were taking the drug trough illicit means — were told that no action would be taken against them if they revealed their identity. From previous experience of such surveys, it was known that the actual figures on the official register did not represent the exact number of addicts. There were probably 10% more addicts not registered, but who obtained supplies through illicit sources. The ratio of registered addicts to the general population in some of these areas was as high as 5%. The total number of addicts traced was 12,460.

Medical Treatment Centres

Treatment of the opium habit was made available in all the government and tea-garden hospitals throughout the whole area of prohibition. As these institutions were not considered sufficient to cope with the rush of addicts in a short period of twelve weeks, additional treatment centres were opened in suitable places. A special staff of forty medical men was also recruited for the campaign and given training in the technique of treatment.

Analytical Study of the Records collected

The records of the various hospitals and treatment centres after the campaign revealed that 10,200 persons presented themselves for treatment within about three months. It was, however, not possible for a comparatively newly trained staff to keep complete records accurately for statistical analysis and research purposes in such a large operation. In 8,000 addicts among those who presented themselves for treatment, reasonable data could, however, be gathered for statistical analysis. The results are given below in tabular form. This was a unique campaign unparalleled in the history of drug addiction anywhere in the world. Therefore, the details given below are not unimportant. A further reason for giving these figures is that they throw considerable light on some important aspects of drug habits generally, and the opium habit in particular, among the people of this country. For instance, (i) factors responsible for drug habits, (ii) intensity of drug addiction and its relations to dosage, (iii) principal withdrawal symptoms and their relative preponderance, (iv) relationship between age of addict, dosage, duration of addiction and success of treatment, have all been clearly brought out.

Firstly, aetiological factors which led to the habitual use of opium in this large series of addicts were analysed. The results are given in Table I.

Categories of Addicts

For the purpose of treatment, the addicts were classified in three groups, according to intensity of addiction as determined by factors such as age, daily dose, duration of addiction, general health, etc. (see Table II).

TABLE I

Factors responsible for the drug habit

Aetiological factor	Number	Percentage
1. Association and example of relatives and friends	2,800	35
2. To alleviate the symptoms of a disease, or as a cure for certain ailments	2,000	25
3. To overcome fatigue	1,600	20
4. For euphoric and pleasure-giving effects.	1,200	15
5. To replace another addiction, such as alcoholism	400	5
TOTAL ...	8,000	100

TABLE II

Classification of 8,000 addicts treated according to intensity of addiction based on factors such as daily dosage, age, duration of addiction, etc.

Number treated in each group	Percentage	Daily dosage in grains	Maximum age in years
Group I, 4,800	60	15 and less	40
Group II, 2,400	30	16 to 30	50
Group III, 800	10	31 and over	70

Group I : Consisted of 4,800 (60%) persons of whom all were below 40 years of age and were taking the drug in doses of less than 15 grains a day. The average duration of addiction in this group was shorter than in groups II and III.

Group II : 2,400, or 30%, in the series who took between 16 and 30 grains a day; the highest age in this group was 50 years.

Group III : The rest of the subjects — i.e., 800, or 10%. Most of them took the drug in doses of over 30 grains a day, and the average duration of addiction was more than in the previous two groups. The maximum age recorded was 70 years.

Withdrawal Symptoms

In spite of the intensive treatment given, withdrawal symptoms were encountered in quite a large number of addicts. The principal symptoms observed are detailed in Table III.

TABLE III

Principal withdrawal symptoms observed, with their relative preponderance in the cases of the different groups

Withdrawal symptoms observed	Group I 4,800	Group II 2,400	Group III 800
1. Pain in the body and limbs, cramps, general malaise, etc.	3,840 (80%)	2,160 (90%)	800 (100%)
2. Vaso-motor disturbances, such as sneezing, running from the eyes and nose	2,880 (60%)	1,920 (80%)	720 (90%)
3. Cardio-vascular manifestations, such as feeble and irregular pulse, sinking sensation, cardiac embarrassment and collapse	960 (20%)	770 (30%)	400 (50%)

TABLE III *(continued)*

Withdrawal symptoms observed	Group I 4,800	Group II 2,400	Group III 800
4. Insomnia	2,880 (60%)	1,920 (80%)	800 (100%)
5. Gastro-intestinal disturbances, such as nausea, vomiting and diarrhoea	960 (20%)	720 (30%)	480 (60%)

In all cases of relapse, the percentage in reduction of dose in each case was recorded. It was not possible to keep a watch over all the persons belonging to Groups I and II. A few in Groups I and II and the majority of addicts treated under Group III who, it was feared, were liable to relapse were kept under observation in their homes for a period varying from 4 to 24 weeks. Results of treatment are summarized in Table IV.

TABLE IV

Results of treatment

Results	Number of addicts	Percentage
1. Complete cure (addicts reclaimed as useful members of society)	3,200	40
2. Reduction in dosage by three-quarters of the original dose	2,400	30
3. Reduction in dosage by half of the original dose	1,600	20
4. Failure of treatment	800 *	10
TOTAL ...	8,000	100

* Six cases died during treatment.

It will thus be observed that 3,200 (40%) of the addicts treated in this experiment were completely cured of the habit when the campaign ended; 2,400 (30%) succeeded in reducing their daily dose by three-quarters of the original; and 1,600 (20%) showed reduction in dosage by half of their original dose. There were 800 (10%) who showed little or no response to the treatment, and amongst these six died during the course of treatment.

TABLE V

Relation between the age of the addicts and the result of treatment

Result of treatment	Age of addicts				Total
	25 years and below	26-40 years	41-60 years	61 years and above	
Complete cure	280	1,500	1,300	120	3,200
Dosage reduced by three-quarters	180	1,030	1,040	150	2,400
Dosage reduced by half ...	60	520	820	200	1,600
Failure of treatment	Nil	80	200	520	800
TOTAL ...	520	3,130	3,360	990	8,000

These results are very interesting. It will be seen that the number of persons cured in groups of older persons was much less than in the case of the younger ages. Thus, out of 3,200 cases who were completely cured, 1,780 were below 40 years of age, 1,300 between 41 and 60 and only 120 persons were above 60 years of age. In this series there were 520 persons below 25 and out of these 280 got rid of the habit completely. There were 3,130 persons between 26 and 40 years, and out of these 1,500 were completely cured. There were 3,360 persons between 41 amd 60, and out of these 1,300 were completely rid of the habit. Amongst the 990 addicts aged above 61 years, only 120 rid thems-lves of the habit completely.

Similarly, reduction of dosage was also more marked in the younger age addicts. Conversely, failure of treatment was more marked in the case of higher age groups. It will be observed that in the 26-40 years age group consisting of 3,130 addicts, treatment failed in 80 cases, while in 990 persons aged above 61, treatment failed in 520 cases — i.e., in more than 60%. Thus, the younger addicts were more amenable to treatment than the older and more confirmed addicts.

TABLE VI

Relation between dosage and treatment

Result of treatment	Dose in grains			Total
	15 and under	16-30	31 and over	
Complete cure effected ...	1,200	1,150	850	3,200
Dose reduced by three-quarters	1,020	750	630	2,400
Dose reduced by half	525	325	750	1,600
Failure.....	98	200	502	800
TOTAL ...	2,843	2,425	2,732	8,000

It will be seen that cures were more marked in the addicts who had been taking smaller doses. Out of 2,843 persons consuming the drug in doses of under 15 grains a day, as many as 1,200 were completely cured as compared with 850 out of 2,732 addicts taking 31 grains and more a day. The reduction in dosage was also well marked in the case of the group taking small doses. Failures were more conspicuous among the group taking large doses. Thus, the results of treatment were encouraging in persons who took below 31 grains of opium a day.

TABLE VII

Results of treatment and duration of addiction

Result of treatment	Duration of addiction in years			Total
	10 years and under	11-20 years	21 years and over	
Complete cure effected ...	2,585	615	10	3,200
Dosage reduced by three-quarters	315	2,065	20	2,400
Dosage reduced by half ...	800	710	90	1,600
Failure.....	200	470	130	800
TOTAL ...	3,900	3,850	250	8,000

It will be seen that there were more cures among addicts of shorter duration, viz., 10 years and under, where out of 3,900 persons 2,585 completely responded to the treatment, as compared with 615 out of 3,850 with 11-20 years' duration and only 10 out of 250 with 21 years' and over duration. Conversely the failures of treatment were more marked in the case of addicts of longer duration and in addiction of over 20 years' duration, out of 250 persons 130 showed no response to the treatment.

Rehabilitation Treatment

It was not possible to organize proper treatment during the stage of rehabilitation for such a large group in a comparatively backward and poor state such as Assam. In only a small number of cases was it possible to arrange for vocational and diversional post-withdrawal treatment, which is so important in rebuilding the shattered personality of confirmed addicts of long standing. The individuals with a nervous diathesis

and those liable to relapse were kept under observation through volunteers and relatives to prevent them from taking to the drug secretly. In order to rehabilitate and train addicts who had been weaned from the drug to a new walk of life and narcotic-free environment, attempts were made to provide diversional therapy by way of gardening and cottage industry such as basket-making, mat-making and other such vocations. Some reverted to the habit during the rehabilitation period, and the treatment had sometimes to be repeated twice. It was not possible for most of them to obtain a diet rich in lecithin on account of the expense it entailed. Addition of vegetables rich in lecithin (such as soya beans) to the diet was helpful in preventing relapses. The period of rehabilitation and rebuilding of personality in certain cases sometimes extended over several months and even up to a year depending on such factors as the personality and character of the addict, his environment, the cause of addiction, the presence of a nervous diathesis, heredity, etc. Patients with a nervous diathesis and with a sense of inhibition, specially the aged with longer duration of addiction, were more liable to relapse. Younger addicts with a stable nervous system, who had taken to the habit by mere association, were easier to treat. If during the rehabilitation period, chronic ailments such as toxic foci, malaria, dysentery etc., were attended to, chances of relapse were considerably reduced.

Persons who were suspected of taking the drug secretly were placed under observation, and their urine was examined for the presence of opium alkaloids.

Summary and conclusion

After a detailed study of the problem, the present authors tried various methods of treatment of drug addicts. The sudden withdrawal method from opium addiction was unsuccessful because there were no special institutes in which addicts could be admitted and treated. Some success was obtained with the slow or gradual withdrawal method. In the case of cannabis and cocaine, the sudden withdrawal method succeeded. Auxiliary treatments, such as the use of atropine, hyoscine and insulin, were tried with little success. Vesicatory treatment of Modinos was not uniformly successful in curing addicts. The lecithin treatment suggested by Ma Wen-Chao gave better results. A modification of this treatment in combination with glucose administered intravenously and by mouth, at the height of abstinence symptoms, gave even better results. Of 200 addicts treated in the Hospital for Tropical Diseases, Calcutta, 70% were cured. At the same time, the rationale of the treatment was worked out. Observations on the blood of addicts showed that there were marked disturbances in fluid equilibrium in the body. This treatment helped in restoring the fluid equilibrium to its previous level.

Unfortunately, for want of proper facilities, it was not possible to gauge the exact degree of ameliorating effects produced by lecithin and glucose, by observations on a control series of addicts side by side. From the general observations made, we have no hesitation in saying that the acute distressing symptoms which followed the withdrawal of the drug were, to say the least, made easily bearable in the large majority of cases. This in itself was an important factor in persuading the addicts to give up the drug. Their mental outloock underwent a remarkable change for the better after the treatment.

With regard to the ultimate results of treatment in the Assam series, the majority of addicts could only be kept under observations for a period varying from four to twenty-four weeks, and our observations recorded here were after this period. Table IV shows that 40% gave up the drug entirely. In another 50%, the dose was substantially reduced; and with the non-availability of opium, they eventually gave it up. Only in 10% of the cases was there complete failure.

It was generally believed that success of the campaign was dut to this treatment.

It will thus be seen that no satisfactory treatment of drug addiction has so far been developed. By administration of lecithin and glucose, the abstinence symptoms are eased and a break in the habit is effected, but this often is not a permanent feature.

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The medical and social problems of khat in Djibouti

The Bulletin *reproduces herewith the main features of information on the question of khat transmitted by the French authorities to the Commission on Narcotic Drugs. In order to throw more light on the problem, it seemed desirable to describe the situation which prevails at Djibouti. An increase in the general disease rate in that city has led the health authorities to conduct a survey which has revealed that the consumption of khat could become a significant social danger. Doctors Guedel, Lafaurie and Marguet, who were in charge of this survey, give the following description of the physiological effects of the consumption of this drug in their report.*

Physiological effects

The following effects were observed in a khat user, the observations being related to his behaviour when in the company of his friends, and using as appropriate the words of the addict or of his family :

Tonic Phase

Mental effects: " We may take such typical cases as a labourer who works all day in the sun in a workyard or a messenger who has shuffled around from one office to another carrying documents. These men, upon leaving their place of work, suddenly become animated and with a set look join the procession of khat addicts and hurry to the shopkeeper on Avenue 13.

" Several men form a group 'chew'; as they do so, a feeling of mental alertness comes over them, they become talkative and understand things which they did not understand before. They become imaginative, discuss matters and respond quickly; other things are forgotten; then their eyes are wide open and their sight slightly blurred, as if they had a veil before their eyes.

" The whole process is in the mind; there is a pleasant sensation of things going round quickly in the head, which is so full of thoughts that it feels as if it may almost burst. The blood that mounts to the head brings thoughts with it, and the khat user can go on thinking all night without feeling sleepy; sleep seems totally unnecessary, and there is no desire to go to sleep. There is a feeling of strength, heavy weights can be easily lifted; movements are effortless and the whole body experiences a sensation of well-being.

" The khat user has no appetite; even if he wants to eat, he is unable to do so; he can swallow nothing but broth, milk and water. Moreover, he becomes thirsty as he chews; his throat is parched, he talks and perspires, which make him all the more thirsty.

" Enjoyment is even greater if cigarettes are smoked; even non-smokers smoke when chewing.

" Tobaco smoke enhances the effects of khat, and the chewer chain smokes, using up a whole pack before leaving."

Cardio-vascular effects: " The blood circulates faster, especially in the head and eyes; it can be felt circulating in the veins and the heart pumps abundantly."

Effects on the sexual functions: " When a man chews khat, he becomes sexually excited and seeks the company of women. But khat has an inhibiting effect on the male, its use generally causing temporary impotence or otherwise impeding the full accomplishment of the sexual act."

Digestive effects: " After chewing khat, the abdomen is hard and slightly swollen.

" Habitual khat chewers suffer from constipation for several days at a time or even a week. As they do not eat, they grow thin, have stomach ache, and sometimes have to be taken to hospital at night because the pain is too great."

Depressive Phase

The tonic phase of khat is followed by the usual depressive phase, which is common in the case of all nerve stimulants.

Those who chew khat only after the morning's labours work harder in the afternoon and are stronger, quicker and more energetic.

At night they sleep well and regain their strength during the depressive phase.

On the other hand, those who chew at night stay up late; they generally take more than the others and that prevents them from sleeping all night. The depressive phase begins in the morning when it is time for them to go to work. They do so reluctantly, cannot bear to talk; sometimes they seem to have grown alarmingly thin, and on occasion they have to be sent to the doctor, who diagnoses the complaint by the brownish-green furry aspect of the tongue.

Therapy

It is quite certain that a fairly large number of people have acquired the habit of taking khat for enjoyment.

" If the plane from Ethiopa is late some day, you can be sure that there are one, two and perhaps three thousand inhabitants of Djibouti who will be looking up at the sky. Some of them do not return home for dinner. Sadly they wait for their khat."

However, that temporary condition is dependent on the addict's power to obtain the drug at a moment's notice; neither the symptoms nor the duration of the condition are comparable with those experienced by drug addicts while deprived of their drug. The desire for khat is not as strong as that for alcohol or tobacco.

The condition is characterized by sadness, bad temper, lethargy, general debility accompanied by physical and mental slackness, and a disinclination to effort, which may last for several hours or days without resulting in any organic disturbance or any serious mental disorder.

The fact that there is no addiction to khat has been confirmed by observations in hospital wards. Most of the hundreds of sick persons who were studied during the survey and treated at the Djibouti hospital for various complaints were khat users who were physically run down and had suddenly been deprived of the drug. After several days in the hospital they began to put on weight in a striking manner and did not seem at all affected by the withdrawal of the drug. They gained weight on a diet of nothing but rice and meat, and their skin became smooth.

Patients questioned by us did not complain of being deprived of the drug; they were glad to be out of the way of temptation and to be able to sleep, eat and put on weight.

Deprivation of khat, therefore, is not associated with any morbid condition. No drug withdrawal psychosis is created. There is no real craving.

On the other hand, there is a neurosis among khat users associated with the knowledge that they have it in their power to indulge in the drug, which seems to be a sort of ecstasy preceding actual consumption.

Social effects

As is well known, khat is a highly perishable substance which is preferably consumed during the first few days after harvesting. It was formerly imported to Djibouti by rail, but since the end of the war it has been almost exclusively imported by air. The drug comes almost exclusively from Ethiopia. A plane brings an average of almost 600 kg of khat every day to Djibouti and also supplies to Aden, from where it is distributed throughout the neighbouring countries. Most of the khat transported by this route is consumed by the population of Djibouti. Very small quantities are delivered to a few villages near the city which can be quickly reached by road. It is primarily the extension of air transport service to Djibouti which has enabled the majority of the 18,000 inhabitants of the city to become khat users.

After 1952, imports reached a level of approximately 21,900 kg per month (i.e., 720 kg per day). The government authorities estimate that an additional amount of 5% of that figure was smuggled into the country, thus bringing the total to approximately 23,000 kg per month, which corresponds to 80,500 bunches (each bunch weighing 280 g). The peak year was 1953, a year of prosperity in which a record total was paid out in wages. The present slight decline actually conceals a steady increase in khat consumption among the population. There is less money available to buy khat, but a larger number of people are consuming it.

A study of khat movements from producer to consumer reveals that it undergoes sudden price rises at certain stages. A bunch weighing 280 g is bought for 20 French Somali francs from the Ethiopian producer, and eventually costs the consumer almost 200 francs. Prices vary from one day to the next, viz.: 180 to 200 francs at the beginning of the month; 160 francs at the end of the month; 200 francs on Sundays; 300 francs on Moslem holidays; and 600 to 800 francs in certain circumstances (such as a strike of importers).

The average price can be considered to be 180 francs per bunch, which we shall take as a basis in estimating the amount of wages spent on khat.

Every month, inhabitants of Djibouti buy more than 80,000 bunches at 180 francs each, which means that a city of 18,000 persons (including women and children) spend nearly 14.4 million francs on the drug; this is a staggering sum, especially when converted into its tangible equivalent in food rations, which is what really counts. The whole khat problem can be resolved into a problem of nutrition. The per capita food budget is naturally hard to estimate. It varies greatly between individuals, depending on their race, social position, dependents and habits. For the population as a whole, it can be determined only approximately on the basis of the average monthly wage.

On the basis of this calculation, it is astonishing to note that the 14.4 million francs which are spent on khat in Djibouti every month represent the equivalent of approximately 8,000 food rations which are sacrificed every day for the purpose of buying the drugs.

The medical consequences of this situation give rise to concern. The incidence of disease is so high that 400 hospital beds are permanently occupied by inhabitants of the city. Out of 130 beds in the medical services which are occupied by men, 110 are occupied by persons suffering from tuberculosis. The number of tubercular patients is considerably higher among the men than among the women. Among the women, the incidence of tuberculosis and pernicious anaemia is about the same. The clinical picture among the children fluctuates, the most common cause of hospital admissions being the early phase of cachexy, or general debility. Khat is clearly the cause of this state of affairs, mainly because it stays the pangs of hunger, as happens in the case of alcoholics, who similarly do not suffer from hunger and fall an easy prey to tuberculosis.

Khat users eventually become physically run down because they eat only occasionally, go without sleep and use up their nervous energy. One day, the entire family will be taken to hospital, the father going to the tubercular ward and the mother and child to an adjoining ward for patients suffering from anaemia and debility caused by malnutrition. When he arrives at the hospital, the khat user has a pink tongue, covered with the brownish fur deposited by the drug; he may not be well nourished, but at least he has an average count of red corpuscles, whereas his wife suffers from anaemia and avitaminosis.

The amount spent on khat by wage-earners represents a big proportion of the family budget. According to individual cases, it can be estimated at 15% to 30% (25% is probably an average figure). This large percentage means, in the first place, that the wage-earner and his family do not receive adequate nourishment. It also has repercussions on the wage problem. Every fluctuation in the retail price of khat automatically leads to wage changes, which are made under some other pretext.

A consequence which is perhaps les sapparent is the degeneration of family life. The husband spends long hours in a cafe or house chewing khat with his friends; his wife is left to shift for herself and bring up her children as best she can. In addition, when the husband comes home late at night the effects of khat have done their work and his virility is generally impaired. In the long run, this type of impotence may lead to a chronic condition requiring medical treatment. As a result, there are frequent and repeated divorces, and marriages hang by a thread. Paternal authority, in such cases, is greatly undermined.

Adolescent boys take to the khat habit at a very early age, and recently a certain number of women have also become addicts.

* * *

On the social level, certain major trends are apparent: Work output is undeniably reduced and this results in a vicious circle; low output means low wages. Similarly, it is surprising to see the lack of initiative and interest which many of these people display in self-improvement. This is all the more surprising because these people are quite intel-

ligent and are far from being intellectually ungifted. It is not unlikely that this situation can be traced to the fact that they devote their leisure time to the consumption of khat, with the resulting impairment of their will-power.

Together with low work output and disinclination to self-improvement, there is also, among the male part of the population, a state actually bordering on mass neurosis. The individual is obsessed by a frantic desire for khat which seems to inhibit aspirations toward higher aims; it makes the man a slave to his vice.

In view of the situation which has been brought about by khat at Djibouti, as objectively described above, the French Government had to consider whether it should continue to regard khat as simply a habit-forming substance. To answer that question, it referred to the definitions approved by the Expert Committee on Addiction-Producing Drugs in its seventh report.*

It was found that khat does not fall clearly within the terms of either of the two definitions of drug addiction and drug habituation. In fact, in the light of the description of the situation prevailing in Djibouti, it can be said that khat falls within the definition of habituation given in the first three paragraphs :

(1) There is a desire (but not a compulsion) to continue taking the drug for the sense of improved well-being which it engenders.

(2) There is little or no tendency to increase the dose.

(3) There is some degree of psychic dependence on the effect of the drug, but absence of physical dependence and hence of an abstinence syndrome.

On the other hand, although there may be some doubt with regard to the theoretical definition of the effects of khat, it is obviously necessary to take energetic steps to combat this social evil without delay.

In view of the urgency of the question, the French Government decided, even before the meeting of the Commission on Narcotic Drugs, to prohibit the use of this plant.

The following decree was passed on 2 April 1957 and published in the *Journal officiel* of 5 April 1957:

...

Art. 1. The Public Health Code (Part II) has been supplemented by a new article R.5166-I, which reads as follows:

" Khat is classified as a narcotic drug.

" The importation, exportation, production, possession, trade in, and use of, khat and preparations containing khat or prepared with a khat base are prohibited.

" For the purposes of this code, ' khat ' means the leaves of the shrub *Catha edulis* (*Celastrus edulis*) of the celastrus family."

Art. 2. Article R.5229 of the Public Health Code (Part II) is supplemented as follows:

" Any quantity of khat or its preparations which are seized in connexion with the violation of the terms of Article R.5166-I shall be destroyed after two samples have been taken which shall be forwarded respectively to the competent judicial authority and to the Central Office for the Repression of the Illegal Traffic in Narcotic Drugs."

Art. 3. The provisions of this decree shall be applicable in Algeria, in the Overseas Territories and in Cameroons.

...

* WHO *Technical Report Series*, 1957, No. 116.

Recent advances in pethidine-type analgesics

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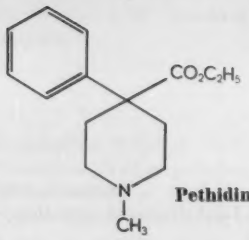
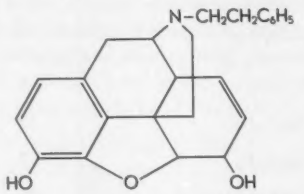


Pethidine

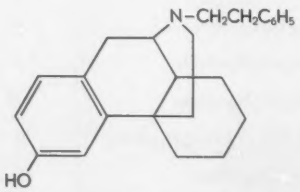
Synthetic analgesics including substances related to pethidine[1] have recently been comprehensively reviewed by Braenden, Eddy & Halbach (1). It is the purpose of this paper to describe important pethidine-type compounds that have been reported since this review and to present detailed information concerning 1 : 3-dialkyl-4-aryl-4-acyloxypiperidines and 7-membered ring analogues of pethidine. A study of structure-activity relationships in this field will also be made.

Replacement of the N-methyl Group of Pethidine and Related Compounds by other Groups

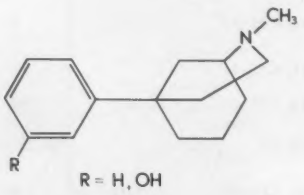
Until recently it was thought that, for optimum activity, the basic group of an analgesic must bear a methyl group and that substitution of this group by higher alkyl, or other groups, must result in a fall in activity (1). That this is not the case has now been shown by the synthesis of several analgesics substituted by the N-2-phenylethyl group (and other groups) that have greater activities than the corresponding N-methyl compounds. Thus N-2-phenylethyl-*nor*morphine (I) and *nor*dromoran (II) are more potent analgesics than their respective parent compounds (2, 3). Perrine & Eddy (4) report that N-2-phenylethyl and N-2-hydroxy-2-phenylethyl*nor*pethidine (III and IV respectively, see flow sheet 2), are both at least twice as active as pethidine. Acetylation of the hydroxy compound giving (V) results in an almost complete loss of activity. Weijlard *et al.* (5) have synthesized N-2-*p*-aminophenyl*nor*pethidine (anileridine, VI) and state that it has several times the activity of pethidine. In a more detailed study, Orahovats *et al.* (6) report that anileridine is ten to twelve times more potent than pethidine in animals, with high oral activity and relatively mild side reactions. May (7), in contrast to the above results, has found that replacement of N-methyl by N-2-phenylethyl in a number of morphine-fragment type compounds (VII and VIII) results in a fall in analgesic potency. Anderson, Frearson & Stern (8), have prepared a series of pethidine analogues of type (IX) in which Y represents an alkyl group carrying a heterocyclic residue X. Several of these compounds show notable activity, and one, morpholinoethyl*nor*pethidine (IX, Y—X = CH_2–CH_2–N⟨O⟩) is three to seven times more potent than pethidine itself (9, 10). When oxygen is replaced by sulphur in the heterocyclic residue (IX, X = N⟨S⟩) activity falls to approximately that of



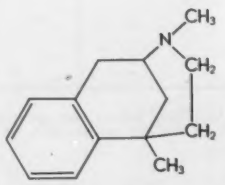
I



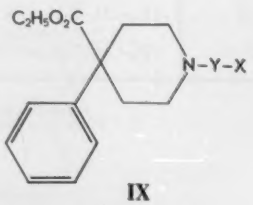
II



VII



VIII

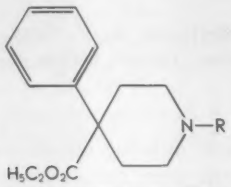


IX

[1] 4-carbethoxy-1-methyl-4-phenylpiperidine, also known as Meperidine and Dolantin.

TABLE 1

Analgesic activities of 1-substituted-4-carbethoxy-4-phenylpiperidines



Compound No.	R	Relative analgesic activity [a] (pethidine = 1)	Reference
1	$-CH_2.CH_2.C_6H_5$	2	4, 66
2	$-CH_2.CH(OH).C_6H_5$	3	4
3	$-CH_2.CH(OCOCH_3).C_6H_5$	0	4
4	$-CH_2.CH_2.C_6H_4p\text{-}NH_2$	10 – 12	5, 6, 66
5	$-CH_2.CH$ -N⟨⟩O	3 – 7	9, 10
6	$-CH_2.CH_2$-N⟨⟩	<0.25	9
7	$-CH_2.CH_2$-N⟨⟩	0	"
8	$-CH_2.CH_2$-N⟨⟩ (C_6H_5, $CO_2C_2H_5$)	0	"
9	$-CH_2.CH_2.Cl$	<0.25	"
10	$-CH_2.CH_2$-N⟨⟩NH	0	"
11	$-CH.CH_2$-N⟨⟩O (CH_3)	1 – 3	"
12	$-CH_2.CH_2.CH_2$-N⟨⟩O	0.5 – 1	"
13	$-CH_2.CH_2$-N⟨⟩$-CH_3$	0	"
14	$-CH_2.CH_2$-N⟨⟩	0	"
15	$-CH_2.CH_2$-N$(CH_2.CH_2OH)_2$	0	"
16	$-CH_2$-N⟨⟩O	0.25 – 0.5	"
17	$-CH_2.CH_2$-N⟨⟩OH	0	"
18	$-CH_2.CH_2$-N⟨⟩S	1 – 2	"
19	$-CH_2-CH_2-C_6H_4m.OH$	1	66
20	$-CH_2-CH_2-C_6H_4m\text{-}OCH_3$	3	"
21	$-CH_2-CH_2-C_6H_4p\text{-}OCH_3$	3	"
22	$-CH_2-CH_2-C_6H_3m\text{-}OHp\text{-}OH$	6	66
23	$-CH_2-CH_2-C_6H_4o\text{-}NO_2$	1	"
24	$-CH_2-CH_2-C_6H_4o\text{-}NH_2$	5	"
25	$-CH_2-CH_2-C_6H_4p\text{-}NO_2$	6	"
26	$-CH_2-CH_2-C_6H_4p\text{-}CH_3CONH-$	7	"
27	$-CH_2-CH_2-C_6H_4p\text{-}(C_2H_5)_2N-$	7	"
28	$-CH_2-CH(CH_3)-C_6H_5$	0.5	"
29	$-CH(CH_3)-CH_2-C_6H_5$	0	"
30	CH_2-CH_2—⟨⟩N	9	"
31	CH_3-CH_2—⟨⟩N	5	"
32	$-CH_2-C_6H_5$	0	"
33	$-(CH_2)_3-C_6H_5$	13	"
34	$-(CH_2)_4-C_6H_5$	2	"
35	$-CH_2CH = CH-C_6H_5$	29	"
36	$-CH_2-C\equiv C-C_6H_5$	0	"
37	$(CH_2)_3$—⟨⟩N	2	"
38	$-CH_2-C_6H_4p\text{-}NO_2$	0	"
39	$-(CH_2)_3-C_6H_4p\text{-}NO_2$	5	"
40	$-(CH_2)_4-C_6H_4p\text{-}NO_2$	0.5	"
41	$-CH_2-CH = CH-C_6H_4p\text{-}NO_2$	10	"
42	$-CH_2-C_6H_4p\text{-}NH_2$	1	"
43	$-(CH_2)_3-C_6H_4p\text{-}NH_2$	6	"
44	$-(CH_2)_4-C_6H_4p\text{-}NH_2$	2	"
45	$-CH_2-CH = CH-C_6H_4p\text{-}NH_2$	12	"

[a] Relative activities have been derived from the results of several independent workers, and thus, as variation occurs both in the methods and test animals used, the figures shown can only serve as an approximate guide.

pethidine whereas compounds lacking oxygen or sulphur in this residue (e.g., X = -N⟨⟩, -N⟨⟩), are practically inactive. Lengthening or shortening of the carbon chain linking the two nitrogen atoms of the two rings results in a considerable reduction of activity; branching also reduces activity, though not sharply.

Elpern *et al.* (66) have recently reported an extensive series of 1-aralkyl-4-carbethoxy-4-phenylpiperidines and obtained the following results :

(1) Replacement of the N-methyl group of pethidine by a substituted phenylethyl group gave compounds of a potency equal to or greater than that of the parent compound. The most potent member of this group was N-*p*-aminophenylethyl*nor*pethidine, having an activity corresponding to that reported for anileridine (6);

(2) Replacement of phenylethyl by pyridylethyl enhanced the potency, with 4-pyridyl being more effective than 2-pyridyl;

(3) Lengthening the distance between the aryl group and the nitrogen atom resulted in peak activity with three methylene groups; in the cases of the 4-pyridyl and *p*-aminophenyl compounds, activity fell on increasing the chain length from 2 to 3 and with the *p*-nitrophenyl compounds the 2 and 3 carbon chain compounds had similar activities (cf. the morpholinoethyl compounds, table 1, in which a similar increase in chain length also results in a loss of potency);

(4) Activity was increased still further when a double bond was included in the 3 carbon chain (the N-cinnamyl analogue is the most active member of the whole series); peak activity in the *p*-aminophenyl and *p*-nitrophenyl compounds was also obtained with a double bond in the carbon chain. Activity was abolished when a triple bond was included;

(5) Chain branching at the β-carbon atom (relative to the nitrogen atom) cut activity by half, while branching at the α-carbon atom abolished activity.

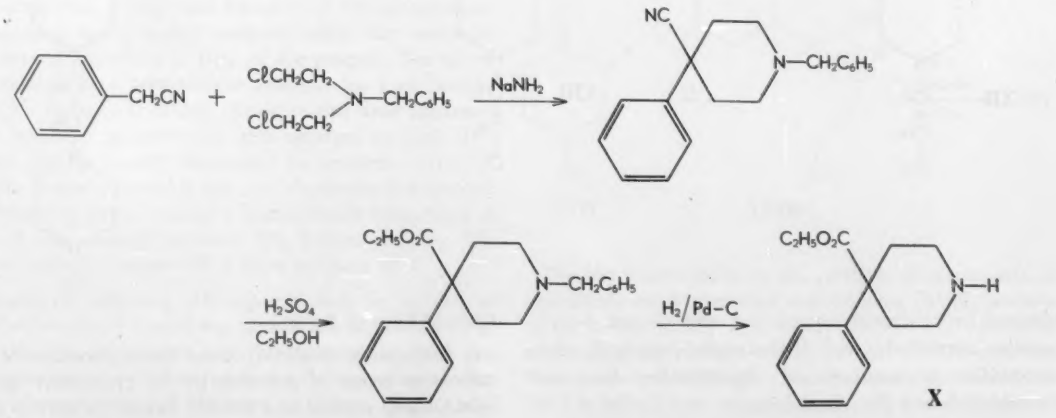
Synthesis

Most of the compounds described in the previous section were prepared by direct N-substitution of *nor*pethidine (X) — an intermediate in one of the commercial methods for the manufacture of pethidine. Flow sheet 1 indicates the synthesis of this intermediate[3] and flow sheet 2 summarizes the synthesis of some of the compounds listed in table 1.

Reaction of the secondary base (X) with phenylethyleneoxide gives 4-carbethoxy 1-(2-hydroxy-2-phenylethyl)-4-phenylpiperidine (IV) which on hydrogenation gives N-2-phenylethyl*nor*pethidine (III) and on acetylation, the ester (V). Weijland *et al.* (5) obtained the 2-*p*-aminophenylethyl analogue (VI) by alkylation of *nor*pethidine with *p*-aminophenylethylchloride hydrochloride in the presence of alkali. The compounds of Anderson *et al.* (8) were obtained by treating *nor*pethidine with the appropriate substituted alkyl halide — e.g., 2-morpholinoethylchloride to give (XI). Where this method proved difficult (compounds 10, 13 and 14 in table 1) the secondary base was first alkylated with ethylene chlorhydrin and the resultant 2-hydroxyethyl compound (XII) converted into the 2-chloroethyl compound (XIII) which reacted readily with heterocyclic bases — e.g., piperazine to give (XIV). The majority of the compounds of Elpern *et al.* (66) were prepared by alkylation of *nor*pethidine with the appropriate alkyl halide; the pyridylethyl compounds were

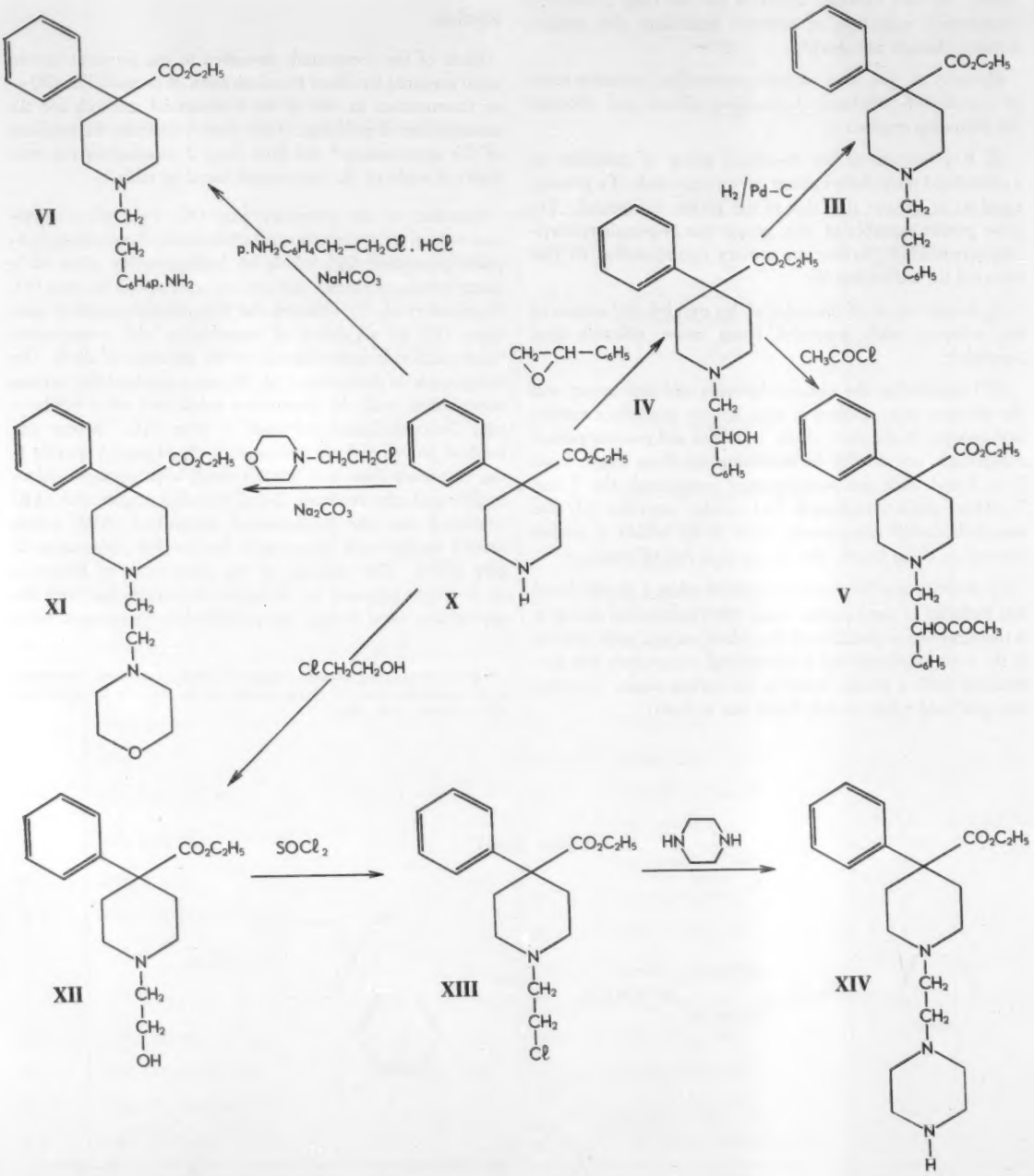
[3] The corresponding N-tosyl compounds are also employed, conversion to the *nor*-compound (X) being carried out in this case by hydrolysis with sulphuric acid. (24)

Flow sheet 1



Flow sheet 2

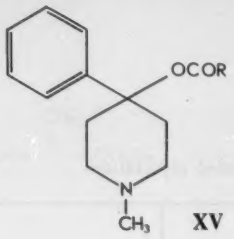
(Synthesis of certain of the compounds listed in table 1)



obtained by condensing *nor*pethidine with 2- and 4-vinylpyridine respectively, and N-(3-phenyl-2-propargyl) ethyl-*nor*pethidine by treatment of the secondary base with formaldehyde and phenylacetylene.

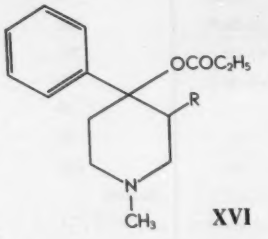
Reversed Esters of Pethidine

In 1943, Jensen *et al.* (11) found that replacement of the carbethoxy group of pethidine by the propionoxy group ($-OCOC_2H_5$) resulted in a fivefold increase in activity over



XV

that of the parent compound. Independently, workers in the Roche Laboratories (12, 13) prepared many compounds of this type (the so-called " reversed esters of pethidine ") and confirmed that the propionoxy compound (XV, R = C_2H_5) gave the most active member of the series.



XVI

The Roche workers found that the substitution of a methyl group into the 3-position of the piperidine ring resulted in a further increase in potency (14). The compound (XVI, R = CH_3) was obtained in two geometrically isomeric forms, designated alpha- and betaprodine respectively,' the latter isomer being resolved into its optical enantiomorphs (29) (for configuration of these isomers, see p. 44). Randall & Lehmann (14) obtained the following pharmacological results in rats, morphine being taken as 100, α-form racemate 97, β-form racemate 550, (+)-β-form 350, (—)-β-form 790. In man, the difference in action between the α- and β-racemates is not so pronounced (16). Gross *et al.* (17) investigated alpha- and betaprodine in man, and Houde *et al.* (18) reported that alphaprodine had a weaker analgesic action than morphine and showed side effects in 10% of the patients. The use of alphaprodine as a postoperative analgesic has been investigated by Bachrach *et al.* (15). Evidence that these substances show addiction properties has been obtained by Isbell (19). Janssen (20) has recently determined the analgesic activity of prodine isomers prepared in our own laboratories and obtained the following results, morphine hydrochloride being taken as 100; in mice, α-form racemate 200, β-form racemate 835, in rats, α-form racemate 190, β-form racemate 3000.

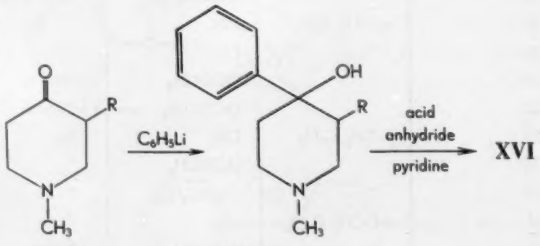
Randall & Lehmann (14) reported that the activity of 3-ethyl-1-methyl-4-phenyl-4-propionoxypiperidine (XVI, R = C_2H_5) (no information concerning isomers is given) was 6.4 times that of morphine while the corresponding acetoxy ester possessed only half the latter's activity. Thus in analgesics of formula (XVI), activity increases in the order (XVI, R = H), (XVI, R = CH_3) and (XVI, R = C_2H_5) — i.e., with increasing size of the 3-substituent. McElvain (21) has synthesized and tested the next higher member (XVI, R = n-C_3H_7) which is stated to have profound activity in rats at doses of 8 mg/kg, but no direct comparison has been made with the lower homologues and it is therefore not possible to draw any conclusions with regard to the optimal size of the 3-substituent from this evidence. Large groups in the 3-position such as benzyl completely abolish activity (21) (see compounds 8-10, 14 and 15, table 2). The acetoxy and butyroxy esters of 1-methyl-3-*n*-propyl-4-phenylpiperidin-1-ol are less active than the propionoxy ester, the latter again representing the most active member of a series.

Inclusion of a double bond into the 3-substituent of XVI results in a highly active compound. This has been shown by the recent report of the analgesic activity of the 3-allyl analogue of prodine — i.e., 3-allyl-1-methyl-4-phenyl-4-propionoxypiperidine (XVI, R = $CH_2CH = CH_2$). Benson *et al.* (69) have found that this compound is approximately ten times as active as alphaprodine with no corresponding increase in its toxicity [details of synthesis have become available subsequent to the submission of this paper for publication (73)].

May (70) has reported structural isomers of alpha- and betaprodine in which the 3-methyl and 4-propionoxy substituents are interchanged. These analogues possess very little analgesic activity.

From information so far available, it appears that the 4-aryl substituent of prodine-type compounds must be a phenyl group if optimum activity is to be attained. In the case of alphaprodine, Randall and Lehman (14) have reported substitution of 4-phenyl by 4-cyclohexyl to result in a considerable fall in activity (see compound 5, table 2), while work in our own laboratories (30) has shown that replacement by *p*-tolyl, *o*-tolyl and *m*-tolyl gives progressively less active substances (see compounds 25, 18 and 22, table 2).

Synthesis

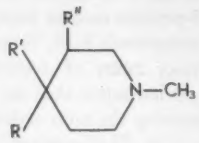


XVII XVIII

The key intermediates in the synthesis of compounds of type (XVI) are 3-substituted 4-piperidones (XVII); reaction of the ketone (XVII) with an aryl lithium and subsequent acylation of the resultant tertiary alcohol (XVIII) gives the " reversed ester " (XVI). The 3-methyl substituted compounds listed in table 2 were prepared from 1 : 3-dimethyl-4-piperi-

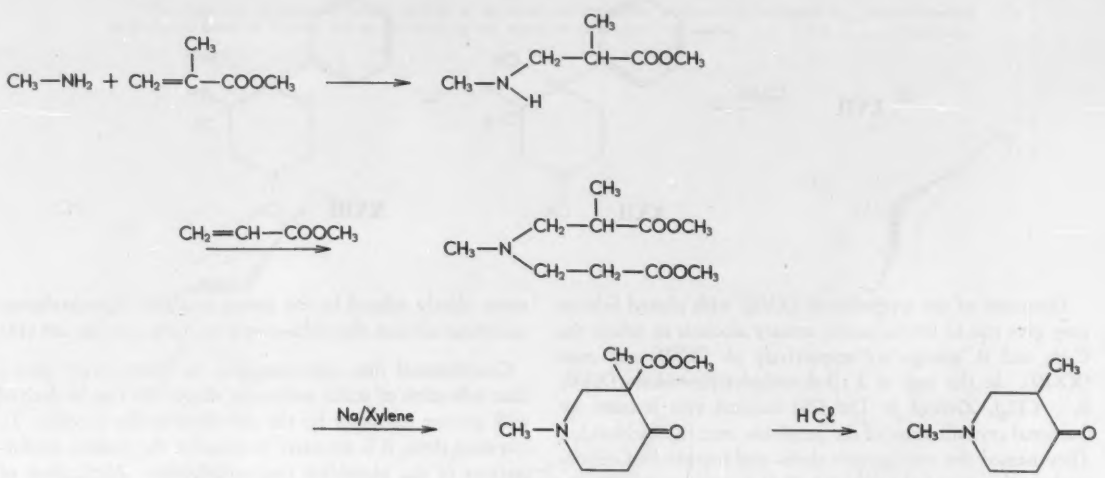
TABLE 2

Analgesic activities of 1-methyl-4-aryl-3 : 4-disubstituted piperidines

Compound No.				*Configuration*[b] (R/R″)	*Analgesic*[a] *activity*	*Reference*
	R	R′	R″			
1	C_6H_5	$OCOC_2H_5$	CH_3	(±)-trans[c]	95	14
2	"	"	"	(±)-cis[d]	550	"
3	"	"	"	(+)-cis	350	"
4	"	"	"	(—)-cis	790	"
5	C_6H_{11}	"	"	—	30	"
6	C_6H_5	$OCOCH_3$	C_2H_5	—	40	"
7	"	$OCOC_2H_5$	"	—	600	"
8	"	$OCOCH_3$	$CH_3.C_6H_5$	—	Inactive	21
9	"	$OCOC_2H_5$	"	—	"	"
10	"	$OCOn\text{-}C_3H_7$	"	—	"	"
11	"	$OCOCH_3$	$n\text{-}C_3H_7$	—	Marked activity at 20 mg/kg	"
12	"	$OCOC_2H_5$	"	—	Profound activity at 8 mg/kg	"
13	"	$OCOn\text{-}C_3H_7$	"	—	Profound analgesia at 32 mg/kg	"
14	"	$OCOCH_3$	$CH_2.CH_2.CON$⬡	—	Inactive	64
15	"	"	$(CH_2)_3OCOC_6H_5$	—	Very weak activity	"
16	$o\text{-}CH_3.C_6H_4$	OH	CH_3	trans	20	30
17	"	$OCOCH_3$	"	trans	70	"
18	"	$OCOC_2H_5$	"	trans	80	"
19	$m\text{-}CH_3.C_6H_4$	OH	"	cis	<20	"
20	"	OH	"	trans	<20	"
21	"	$OCOCH_3$	"	trans	<20	"
22	"	$OCOC_2H_5$	"	trans	50	"
23	$p\text{-}CH_3.C_6H_4$	OH	CH_3	trans	<15	"
24	"	$OCOCH_3$	"	trans	30	"
25	"	$OCOC_2H_5$	"	trans	150	"
26	$o\text{-}OCH_3.C_6H_4$	OH	"	trans	<20	"
27	"	$OCOCH_3$	"	trans	30	"
28	C_6H_5	$OCOC_2H_5$	$CH_2\text{–}CH = CH_2$	—	1000	69
29	"	CH_3	$OCOC_2H_5$	—	3	70

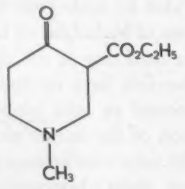
[a] Relative to morphine (=100) unless otherwise stated (footnote to Table 1, also applies to Table 2).
[b] Where details reported.
[c] alphaprodine.
[d] betaprodine.

Flow sheet 3



done (XVII, R = CH_3); Howton's preparation of this ketone, a modification of the usual 4-piperidone synthesis (22), is outlined in flow sheet 3.

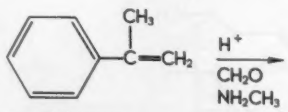
This method cannot serve as a general procedure for the preparation of higher 3-alkylhomologues as the necessary substituted acrylic esters are not readily available. Treatment of 3-carbethoxy-1-methyl-4-piperidone (XIX) with an alkyl



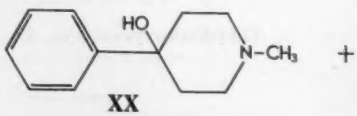
XIX

halide leads, as shown by McElvain (23) and confirmed in our own laboratories, to an N- rather than a C-alkylated product. C-alkylation is possible once the basic nature of the nitrogen atom of the 4-piperidone is masked; thus McElvain (23) has C-alkylated 1-benzoyl-3-carbethoxy-4-piperidone. The ketone (XIX) has been successfully C-allylated and benzylated by treatment with allyl and benzyldimethylanilinium bromide respectively (21). Decarboxylation (prior reduction of allyl to propyl is necessary) of the products leads to the 3-*n*-propyl and 3-benzyl ketones (XVII, R = *n*-C_3H_7 and -$CH_2C_6H_5$ respectively), from which compounds 8-13 in table 2 were prepared.

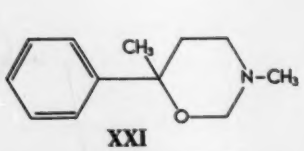
Recently, a new one-stage synthesis of the parent alcohol of the reversed ester of pethidine has been reported (25). The method involves the amino-methylation of α-methylstyrene by means of a methylamine hydrochloride-formalin mixture and gives the 4-piperidinol (XX) in 30% yield together with a substituted oxazine (XXI) as the major product. A modification of the method, employing N, N′, N″ -trimethyltrimethylenetriamine gives the reversed ester itself in 30% yield (26); use of higher α-substituted styrenes leads to prodine and its analogues (67).



α-methyl styrene

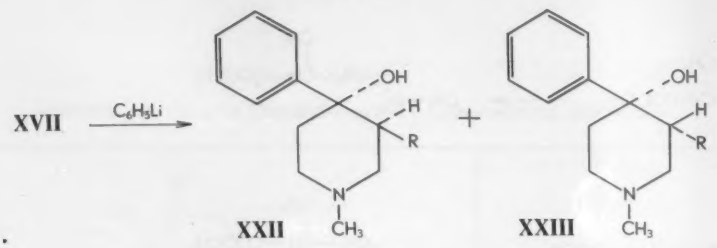


XX

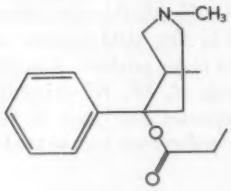


XXI

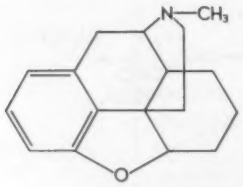
Stereochemistry



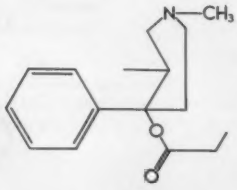
Treatment of the 4-piperidone (XVII) with phenyl lithium may give rise to two isomeric tertiary alcohols in which the C_6H_5 and R groups are respectively *cis* (XXII) and *trans* (XXIII). In the case of 1 : 3-dimethyl-4-piperidone (XVII, R = CH_3), Ziering & Lee (29) isolated two isomers by fractional crystallization of the propionic ester hydrochlorides. They named the two isomers alpha- and betaprodine respectively and assigned the *cis* (CH_3/C_6H_5) configuration to the alpha- and the *trans* (CH_3/C_6H_5) to the beta-compound. These assignments were not rigidly established and were stated to be based upon the easier break-down of the alpha-isomer under hydrolytic conditions and upon the pharmacological results, presuming the more active beta-isomer to be more closely related to the potent analgesic dihydrodeoxymorphine -D than the alpha-isomer as shown on the left (14).



trans (beta-isomer ?)



Dihydrodeoxymorphine -D



cis (alpha-isomer ?)

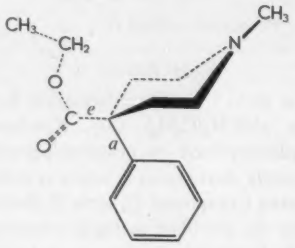
Conventional line representations, as above, may give a false indication of actual molecular shape; this can be derived with greater reliability by the aid of molecular models. To construct these, it is necessary to consider the possible conformations of the piperidine ring substituents. Application of the principles of conformational analysis leads to (XXIV) and (XXV) as the most probable conformations of the *cis* and *trans* isomers respectively (see Fig. 1). Comparison of these models with that of morphine (XXVI) (see Fig. 1) and a consideration of "fit" at a proposed receptor surface first led the present authors to question Ziering & Lee's configurational assignments (27). Of the two isomers, the three-dimensional arrangement (XXIV, *cis* CH_3/C_6H_5) bears the greater resemblance to morphine and would therefore be expected to represent the more analgesically active isomer (betaprodine), while the less active isomer (alphaprodine) is represented by (XXV, *trans* CH_3/C_6H_5).

Support for the reversal of the original configurational assignments is provided by hydrolysis studies on alpha- and betaprodine. The rate of hydrolysis of betaprodine has been shown to be greater than that of the alpha-compound (28); the former must therefore have an equatorial (as in XXIV) and the latter compound an axial propionoxy group (as in XXV). Consideration of the isomer ratios obtained experimentally leads to the same conclusion — the original workers (29) obtained an alpha : betaprodine ratio of 1.4 : 1, and Beckett *et al.* (30) obtained 3 : 1. The stereochemistry of addition of lithium aryls to the piperidone (XXVII) favours approach of the aryl group from the least hindered side of the molecule — i.e., attack from side (*b*) will be preferred to attack from side (*a*) (see XXVII), and in the product, the predominating isomer will have an equatorial aryl group. If these arguments are correct, increase in size of the aryl addendum should favour attack from side (*b*) to an even greater degree. Our own results bear out this contention; treatment of the ketone (XXVII) with *m*- or *p*-tolyl lithium gives isomeric pairs of compounds in which one isomer predominates, whereas addition of the highly hindered *o*-tolyl or *o*-methoxyphenyl lithium results in the formation of one isomer exclusively. Evidence for the configurational identity of the isomers formed in major amount in the addition of

FIGURE 1 — **Diagrammatical representation of the three-dimensional arrangement of analgesics and the "analgesic receptor surface".**

The diagrams represent the lower surfaces of the drug and the upper surface of the receptor- i.e., complementary surfaces. In front of, behind, and in the plane of the paper are represented by ▬, ..., and ___ respectively.

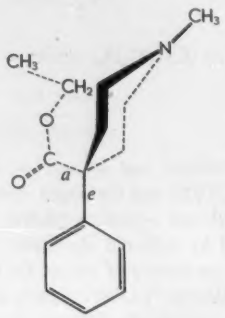
A



LXIV

Pethidine
(axial-phenyl conformation)

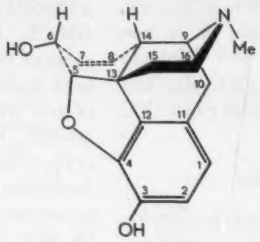
B



LXV

Pethidine
(equatorial-phenyl conformation)

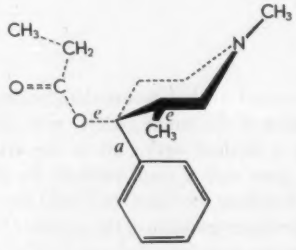
C



XXVI

Morphine

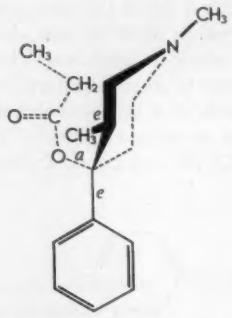
D



XXIV

Betaprodine

E

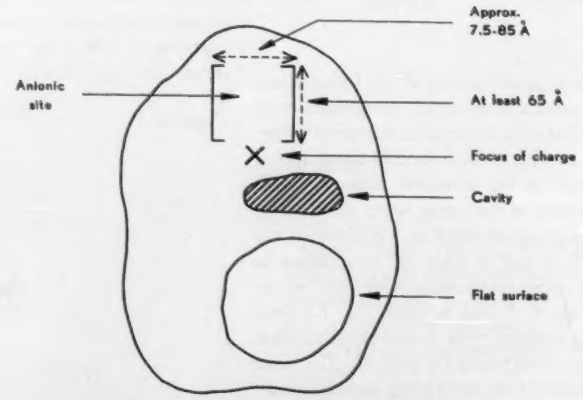


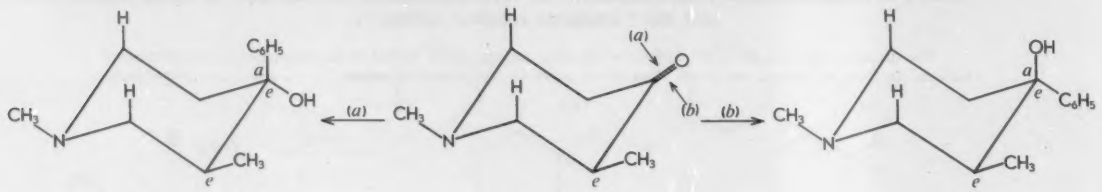
XXV

Alphaprodine

F

Receptor surface



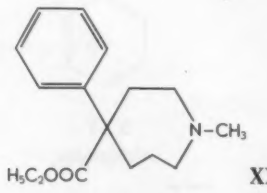


cis (CH_3/C_6H_5) isomer **XXVII** *trans* (CH_3/C_6H_5) isomer

phenyl lithium and *m*- and *p*-tolyl lithium to the piperidone (XXVII) and the single isomers formed upon addition of *o*-tolyl and *o*-methoxyphenyl lithium to this ketone, is provided by infra-red absorption measurements. The latter reveal a consistency of pattern for these isomers in the regions 990 to 1,020 cm^{-1}, 1,350 to 1,385 cm^{-1} and 2,670 to 2,780 cm^{-1}, which is completely different from that shown by isomers formed in minor amount upon addition of phenyl lithium and *m*- and *p*-tolyl lithium to the piperidone (XXVII). This evidence is presented in greater detail in a recent paper (30).

Azacycloheptanes related to Pethidine

Glassman & Seifter (31) have recently described the analgesic activity of a series of azacycloheptanes (hexamethyleneimines) related to pethidine. They found, in general, that replacement of the six-membered ring of pethidine and related compounds by a seven-membered one results in at least a 50% loss in analgesic potency. The straight pethidine analogue (XXVIII, compound I, table 3) is about one-third as

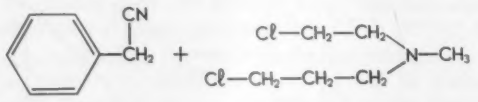


XXVIII

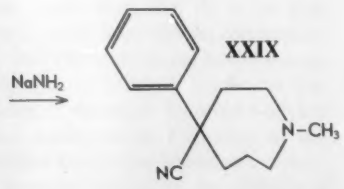
active as pethidine; various modifications of the 4-phenylazacycloheptane molecule gave a number of compounds with analgesic potency equivalent to or better than that of pethidine. Changes in potency as a result of such modifications appear to parallel similar changes in the pethidine molecule itself. The most active compounds in this series were obtained by substitution of a methyl group in the 2 or 3 position of the ring (e.g., compounds 2, 3 and 7, table 3); substitution in the 5, 6 or 7 positions gave compounds with little or no activity (e.g., compounds 4, 5 and 6, table 3). Reversal of the carbethoxy group coupled with 3-methyl substitution gave the prodine analogue (compound 18, table 3). The latter was the most active member of the series being approximately ten times as active as pethidine; its configuration is provisionally reported as *cis*(CH_3/C_6H_5) (32). Ketobemidone (1-methyl-4-*m*-hydroxyphenyl-4-propionylpiperidine) is stated to be approximately thirty times as active as pethidine; the analogue in this series (compound 22, table 3) shows only a twofold increase over the pethidine analogue (compound 1, table 3). Although the latter is less active an analgesic than some of the other members of this series, its clinical use has been studied in detail as it appears to be without certain of the undesirable side-effects of morphine and pethidine (33-35). Fraser (71) reports that the addictive potentialities of the pethidine analogue and certain 1 : 2 - and 1: 3-dimethyl derivatives (compounds 1, 3 and 7, table 3) are either low or non-existent, while the alphaprodine analogue (compound 18, table 3) has addiction liability equal to that of pethidine and approaching that of morphine.

Synthesis

Synthesis of 4-cyano-1-methyl-4-phenylazacycloheptane (XXIX) by condensation of the amine (XXX) with phenylacetonitrile — i.e., by a method analogous to the synthesis of pethidine cyanide, gave only a small yield of the desired product. Flow sheet 4 outlines the reactions finally employed by Diamond (32, 68) for the preparation of the cyanide (XXIX) and its conversion into the pethidine analogue (XXVIII) and the ketone (XXXI). A similar synthesis has been reported by Blicke & Tsao (36).

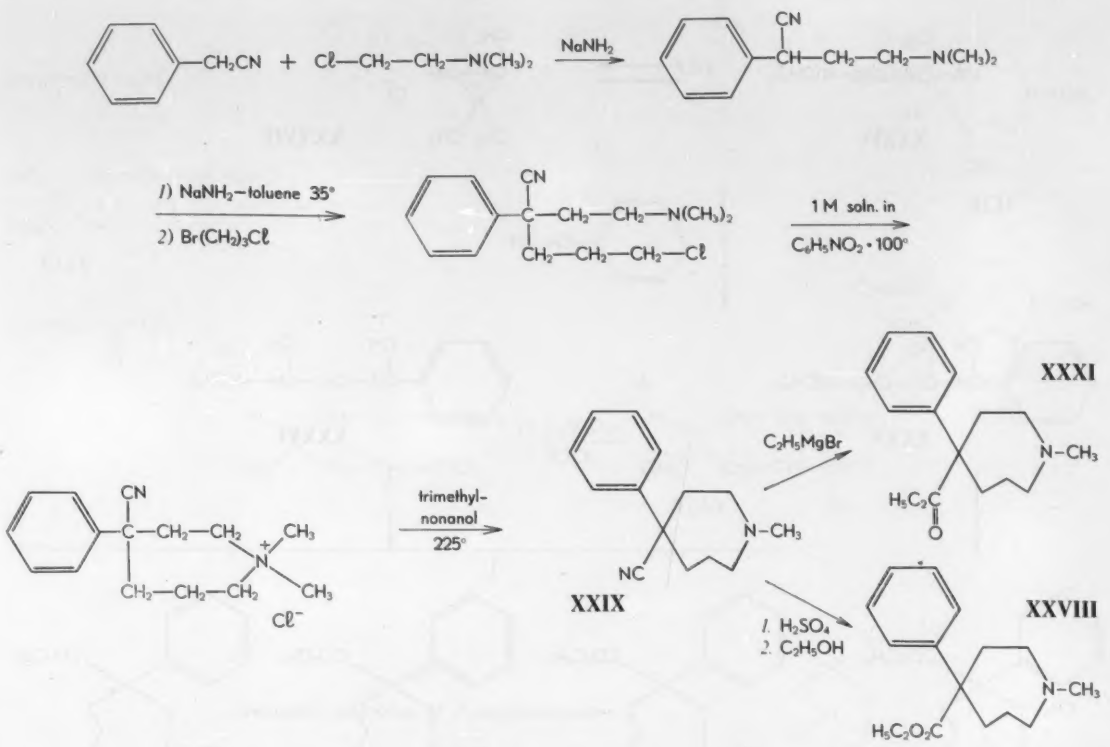


XXX

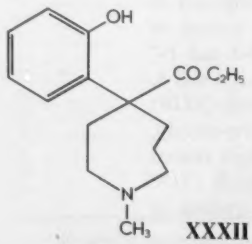


XXIX

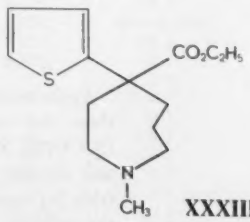
Flow sheet 4



The pethidine analogue (XXVIII) has been resolved via the menthyl ester diastereoisomers and also by crystallization of the (+)-acid tartrates. Diamond (32) states that preliminary reports indicate that most of the analgesic activity of the racemic mixture may reside in one of the isomers. Modifications of the above synthesis employing *m*-methoxyphenylacetonitrile and 2′-thienylacetonitrile gave the ketobemidone analogue (XXXII, compound 22, table 3) and 4-(2′-thienyl)-4-carbethoxy-1-methylazacycloheptane (XXXIII, compound 23, table 3) respectively.

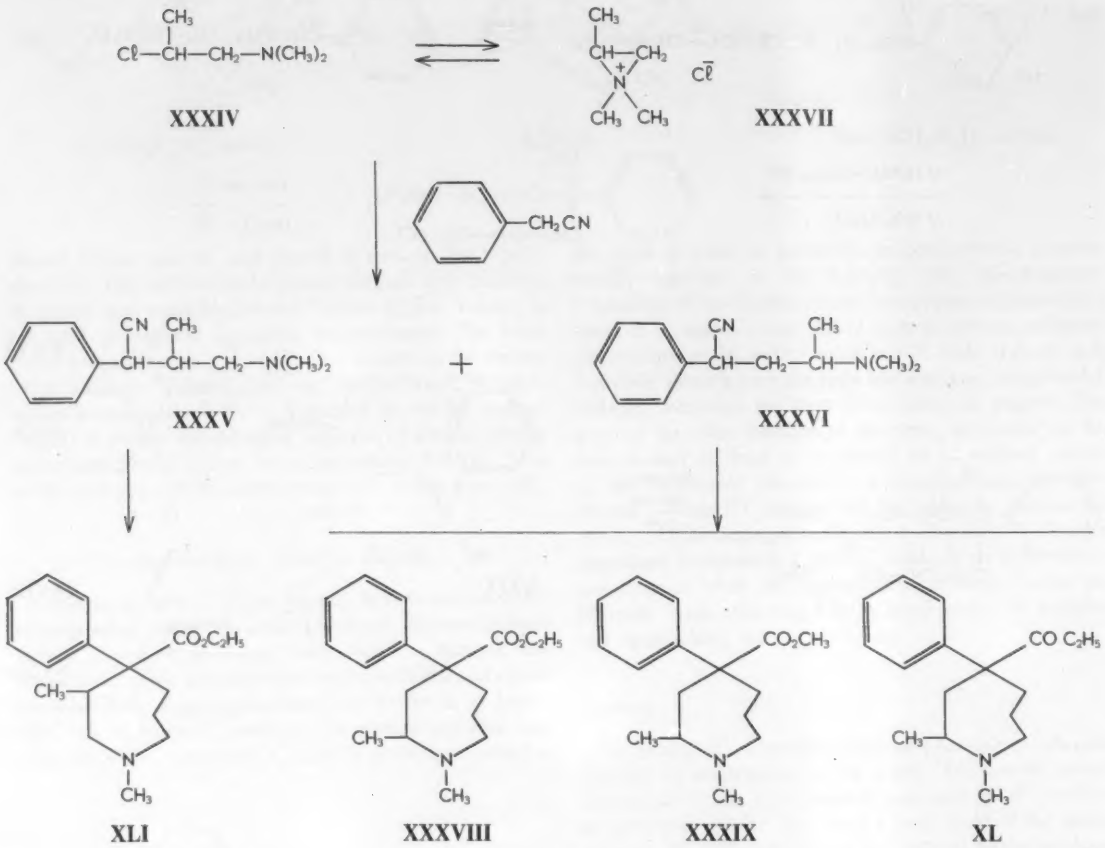


XXXII



XXXIII

Condensation of 1-dimethylamino-2-chloropropane (XXXIV) with phenylacetonitrile yields a mixture of two isomeric cyanides (XXXV and XXXVI) probably owing to the intermediate formation of an ethyleneiminium salt (XXXVII) [c.f. the synthesis of methadone and isomethadone cyanides (37)].



Application of the general synthesis (see flow sheet 4) to these two cyanides leads to the 1-2 dimethyl compounds (XXXVIII, XXXIX and XL, compounds 2, 7 and 13, table 3) and to the 1-3 dimethyl compound (XLI, compound 3, table 3); complications in the synthesis arise on account of the existence of diastereoisomeric forms. The 1-5 and 1-7 dimethyl compounds (XLII and XLIII, compounds 4 and 6, table 3) were obtained by condensation of the cyanide (XLIV) with crotonaldehyde and methyl vinyl ketone respectively. The products, after reduction to the alcohols, were treated with thionyl chloride to give the chlorocompounds (XLV and XLVI); the latter were used in the general synthesis as before.

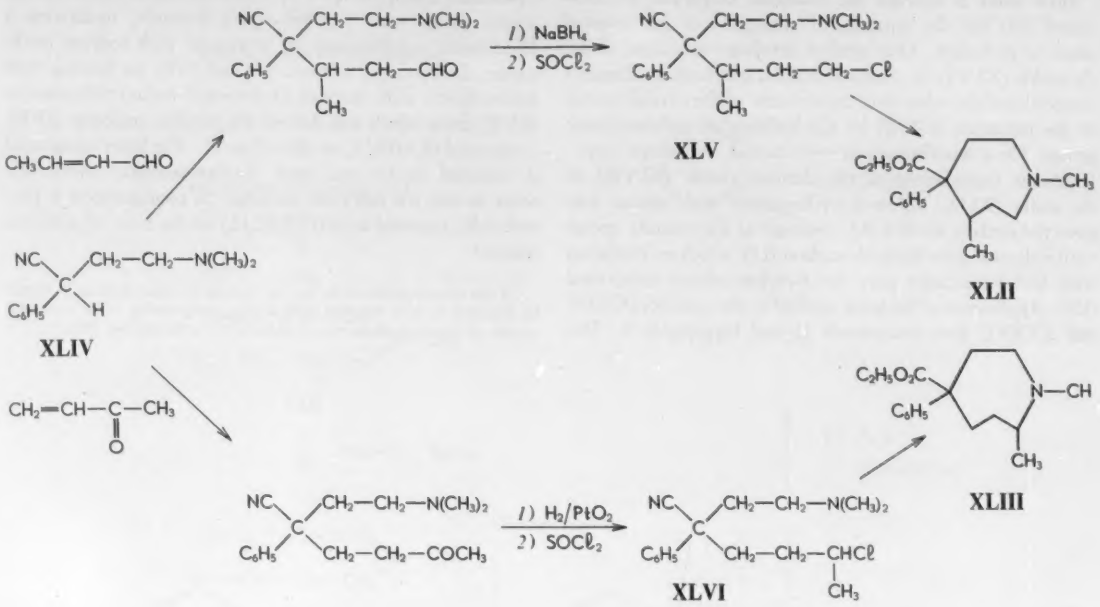


TABLE 3

Analgesic activities of Azacycloheptanes

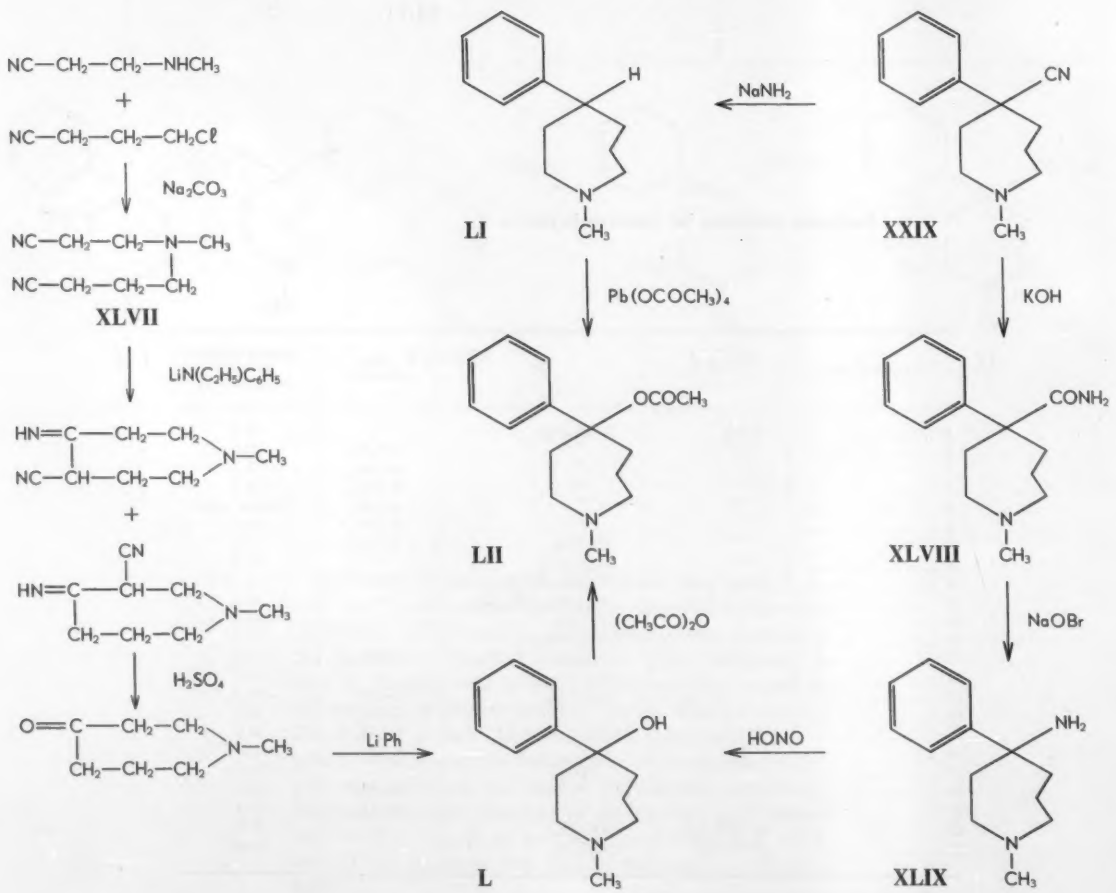
Compound No.	R	R'	*Ring substituents*	*Relative analgesic activity* [a] (pethidine = 1)
1	C_6H_5	$CO_2C_2H_5$	—	0.3
2	"	"	2-CH_3	0.9
3	"	"	3-CH_3	2.3
4	"	"	5-CH_3	<0.3
5	"	"	6-CH_3	Almost none
6	"	"	7-CH_3	<0.2
7	"	CO_2CH_3	2-CH_3	1.1
8	"	$CO_2C_3H_7n$	"	0.3
9	"	$CO_2CH(CH_3)_2$	"	1.1 to 0.3
10	"	$CO_2(CH_2)_2N(C_2H_5)_2$	—	0.3
11	"	COC_2H_5	—	<0.2
12	"	COC_3H_7n	—	<0.2
13	"	COC_6H_5	2-CH_3	0.6
14	"	$SO_2C_2H_5$	—	0.3
15	"	$OCOCH_3$	2-CH_3	<0.3
16	"	"	3-CH_3	0.2
17	"	$OCOC_2H_5$	2-CH_3	0.6
18	"	"	3-CH_3	10
19	"	H	—	None
20	"	"	2-CH_3	<0.3
21	"	"	3-CH_3	<0.3
22	*m*-OH.C_6H_4	COC_2H_5	—	0.7
23	2'-thienyl	$CO_2C_2H_5$	—	None

[a] Measured in rats by intraperitoneal injection.

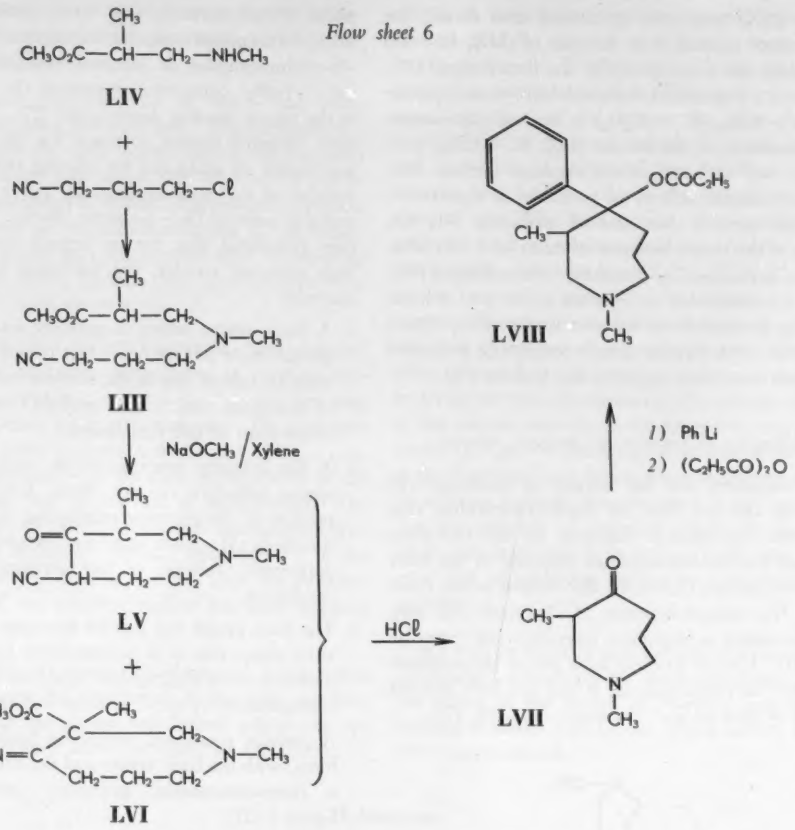
Flow sheet 5 outlines the reactions employed by Diamond (32) for the synthesis of analogues of the reversed esters of pethidine. One method involves cyclization of the dicyanide (XLVII) by means of lithium ethylanilide (Ziegler's method) and the other two, replacement of the cyanide group of the precursor (XXIX) by the hydroxy or carbomethoxy group. These transformations were carried out in two ways : Hofmann degradation of the derived amide (XLVIII) to the amine (XLIX) followed by treatment with nitrous acid gave the tertiary alcohol (L); cleavage of the cyanide group with sodamide gave the hydrocarbon (LI), which on oxidation with lead tetraacetate gave the 4-carbomethoxy compound (LII). Application of the latter method to the cyanides (XXXV and XXXVI) gave compounds 15 and 16 in table 3. The cyanoester (LIII), obtained by condensation of the secondary amine (LIV) with γ-chloro-*n*-propylcyanide, underwent a Dieckmann condensation on treatment with sodium methoxide; the resultant mixture (LV and LVI), on heating with hydrochloric acid, gave 1 : 3-dimethyl-4-azacycloheptanone (LVII), from which was derived the prodine analogue (LVIII, compound 18, table 3; see flow sheet 6). The latter compound is believed to be one pure diastereoisomeric form (the other isomer has not been isolated); its configuration is provisionally reported as *cis* (CH_3/C_6H_5) on the basis of pyrolysis studies.[3]

[3] If this isomer proves to be the one formed in major amount, it would be expected to have the *trans* (CH_3/C_6H_5) configuration from a consideration of the stereochemistry of addition to cyclic ketones (30).

Flow sheet 5



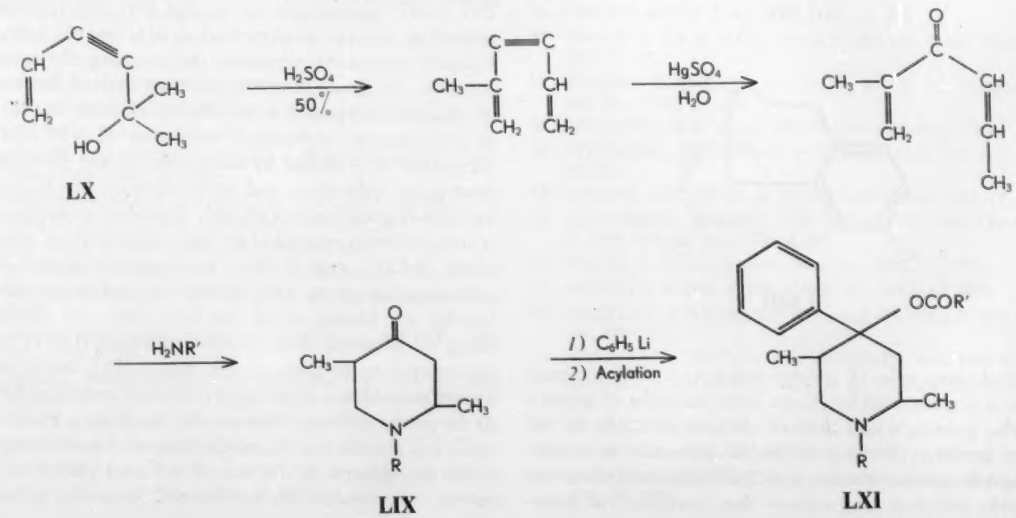
Flow sheet 6



Note on Promedol

Nazarov has reported the synthesis of a series of 4-piperidinol esters derived from 1-alkyl-2 : 5-dimethyl-4-piperidone (LIX). Ketones of this type are obtained from technically available dimethylvinylethinylcarbinol (LX) as indicated in flow sheet 7 (38).

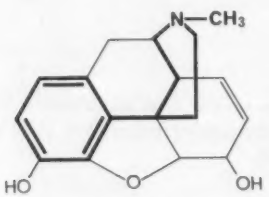
Flow sheet 7



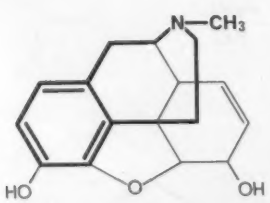
The ketone (LIX) may exist in *cis* and *trans* forms, but attempts at isomer separation in the case of (LIX, R = H) have yielded only one form (probably the *trans* isomer) (39). Promedol, 1 : 2 : 5-trimethyl-4-phenyl-4-propionoxypiperidine (LXI, R = CH_3, R′ = C_2H_5) is one of the isomers obtained by treatment of the ketone (LIX, R = CH_3) with phenyl lithium and acylation of the resultant tertiary alcohols (40). The analgesic activity of promedol is reported to be several times greater than that of pethidine (41, 42). Further details of the stereochemistry of esters of 1 : 2 : 5-trimethyl-4-phenylpiperidinol have recently been published (43); a stereoisomer, isopromedol, is reported to be 2 to 3 times more active than promedol and has been approved for clinical use in the USSR (44). Further details concerning promedol have been given in a recent paper in this bulletin (72).

The Relationship of Structure to Analgesic Activity

It has been suggested that the activity of pethidine-type analgesics lies in the fact that the 4-phenylpiperidine ring system represents an essential fragment of the morphine nucleus and that the three-dimensional structure of the latter is simulated more or less closely by the various active compounds (45). The azacycloheptanes of Diamond (32) may similarly be considered as morphine fragments (see formulae LXII and LXIII). Recent workers have placed less emphasis upon the need for the piperidine ring as such and have stressed the importance of over-all spatial configuration (46, 47).



LXII



LXIII

The decisive role of stereochemical factors in analgesic action is demonstrated by (1) the many examples of enantiomorphic pairs in which most of the activity resides in one of the isomers; (2) the considerable differences in activity amongst the prodine isomers; and (3) the relationships between analgesics and their antagonists — thus morphine and nalorphine [N-allyl*nor*morphine] have identical configurations; levorphan, a potent analgesic, is antagonized by (—)-3-hydroxy-N-allylmorphinan of identical configuration, but not by the (+)-allyl compound possessing the same configuration as the almost inactive dextrorphan (27). The present authors have obtained further evidence for the configurational requirements of analgesics by relating the configuration of a number of the more analgesically active isomers of enantiomorphic pairs to D-(—)-alanine (48–50). From this evidence they postulated that, for an organic compound to exhibit high analgesic activity, the following essential features are necessary :

1. A basic centre which is partially ionized as a cation at physiological pH, in order that it may be able to associate with an anionic site in the receptor surface. A proportion of unionized molecules is probably necessary to facilitate penetration of cell membranes.
2. A flat aromatic structure in the molecule to allow of a strong collective van der Waals' force bonding to a flat portion of the receptor reinforcing the ionic bond mentioned in (1), which otherwise would not be sufficiently permanent, because of ion exchange under biological conditions.
3. The basic group and the flat structure to be almost in the same plane; this to be accomplished by a completely rigid molecule or a slightly less rigid one held in the correct configuration by steric or other constraints.
4. A suitably positioned projecting hydrocarbon moiety to form, with the basic centre and the flat aromatic structure, a three-dimensional geometric pattern indicated in figure 1 (27).

Active analgesics were shown to have structures which enable them to present similar surfaces to allow of their association with a proposed "analgesic receptor surface" (see Fig. 1).

Both pethidine (pKa′ 8.72) (51) and alphaprodine (pKa′ 8.73) (51) satisfy requirement (1) in that they are substantially ionized as cations at physiological pH, and in both, the 4-phenyl substituent represents the necessary flat aromatic structure. Evidence of stereospecificity derived from study of analgesic antagonists is abundantly available in the case of pethidine-type compounds (references 52 — 59 relate to antagonism of pethidine by nalorphine, 54 and 55 to alphaprodine by nalorphine, and 60 to alphaprodine by (—)-3-hydroxy-N-propargylmorphinan). Pethidine probably exists as an equilibrium mixture of the two conformational arrangements (LXIV) and (LXV), the equatorial-phenyl form predominating owing to its greater thermodynamic stability (see fig. 1). Models reveal that both forms are capable of fitting the proposed receptor surface, although (LXIV) would be expected to fit more closely than (LXV), owing to its greater resemblance to the rigid morphine structure (XXVI). As the energy difference between the two forms is likely to be small, it is possible that the stability imparted upon absorption at the site, greatest in the case of the axial phenyl conformation, may override the non-bonded interaction factors in

the molecule itself in determining the conformation of pethidine at the site of action (similar arguments apply to the reversed esters of pethidine).

The most probable conformations of alpha- and beta-prodine have already been discussed (see " Stereochemistry " on p. 44). Models show that both isomers can fit the proposed receptor site, but of the two forms, the *cis* (Me/Ph) should fit better than the *trans* (Me/Ph) isomer. It is possible to explain the increase in activity of compounds obtained by the substitution of a 3-alkyl group into the reversed ester of pethidine in terms of a more bulky hydrocarbon moiety improving the fit in the cavity of the receptor site.

In a recent paper, Beckett, Casy & Harper (61) have advanced the hypothesis that oxidative dealkylation to produce *nor*-compounds at the " analgesic receptor site " is the first step in the reaction sequence leading to analgesia. The influence of the basic group upon analgesic activity may thus be considered from two aspects — (1) the steric requirements of the anionic receptor site, and (2) the ease of dealkylation. The activity of a series of methadone- and thiambutene-type analgesics has been shown to decrease upon increase in the " effective width " of the basic group, and from this evidence the anionic site of the receptor surface has been assigned certain dimensions (62).

The high activity of certain N-substituted *nor*pethidine compounds must now be considered in the light of these facts. Evidence that the phenyl and benzyl groups are too large to fit at the anionic site is provided by the absence of activity in *nor*pethidine-type compounds bearing these substituents upon the nitrogen atom (1, 66). Increase of the chain length giving the N-phenylethyl compound results in an increase in activity over that of the parent compound. The steric limitations of the anionic site must therefore be less restricted farther removed linearly from the focus of charge, and may allow of additional van der Waals' force bonding between the aromatic ring at the end of the chain and the receptor site. The high activity of β-morpholinoethyl *nor*-pethidine and its sulphur analogue may be explained in a similar way, additional bonding being provided in these cases by the lone-pair electrons on the oxygen and sulphur atoms respectively (cf. the increased activity of the morpholino analogue of methadone over its parent compound (63)). The effect of chain branching upon activity may also be interpreted in terms of steric limitations at the anionic site. Branching at the carbon atom α- to the piperidine ring nitrogen atom results in a greater reduction in activity than does branching at the β-carbon atom, where steric limitations are not so great. In addition to these steric factors it is also necessary to stress that the presence of electrical dipoles in the β-phenylethyl chain, etc., may result in an increase in the rate of dealkylation over that of pethidine leading to a consequent increase in activity.

We wish to thank Wyeth Laboratories for making available information concerning the azacycloheptanes. We also thank the editor of the *Journal of Pharmacy and Pharmacology* for making available copies from which certain diagrams in the text were prepared.

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Status of multilateral narcotics conventions

A tabular statement concerning the multilateral narcotics treaties generally based on the table " Status of Multilateral Conventions of which the Secretary-General acts as Depositary ", annexed to document ST/LEG/3, prepared by the Legal Office of the United Nations. The statement has been brought up to date on the basis of information received up to 15 November 1957.

SYMBOLS

× = State having signed without reservation as to acceptance or deposited instrument of ratification, accession or acceptance

s = signature subject to ratification or acceptance

r = reservation

★ = agreement in force

Country	• Protocol of 11 December 1946	• International Opium Convention of 1912	• International Opium Convention of 19 February 1925, as amended	• International Opium Convention of 19 February 1925	• Convention of 13 July 1931, as amended	• Convention of 13 July 1931	• Convention of 26 June 1936, as amended	• Convention of 26 June 1936	• Protocol of 19 November 1948	Protocol of 23 June 1953
Member states of the United Nations										
Afghanistan	×	×	×		×	×			×	
Albania	×	×			×	×			×	
Argentina	×	×	×	×	×	×			s	
Australia	×	×	×	×	×	×			×	×
Austria	×	×	×	×	×	×	×		×	
Belgium	×	×	×	×	×	×	×	×	×	
Bolivia	×	×	×	×r					s	
Brazil	×	×	×	×	×	×	×	×	s	
Bulgaria		×		×		×				
Burma		×[1]		×[1]		×[1]			×	
Byelorussian SSR	×								×	
Cambodia		×[2]	×[2]		×[2]		×			×
Canada	×	×	×	×	×	×	×	×	×	×
Ceylon						×[3]			×	
Chile	×	×	×	×	×	×			s	×
China	×	×		×	×	×	×	×	×	×
Colombia	×	×	×	×	×	×	×	×	s	×
Costa Rica	s	×		×		×			s	s
Cuba	s	×		×		×				×
Czechoslovakia	×	×	×	×	×	×			×	
Denmark	×	×	×	×	×	×			×	×
Dominican Republic	×	×	×	×	×	×			s	s
Ecuador	×	×	×	×	×	×			s	×
Egypt	×	×	×	×	×	×	×	×	×	×
El Salvador		×		×		×r			s	
Ethiopia		×	×		×		×		×	
Finland	×	×	×	×	×	×			×	
France	×	×r	×	×r	×	×r	×	×	×	×
Ghana [4]										
Greece	×	×	×	×	×	×	×	×	×	s
Guatemala	s	×				×		×	s	×
Haiti	×	×	×	×	×	×	×	×		
Honduras	×	×	×	×	×	×			s	
Hungary	×	×	×	×	×	×			×	
Iceland		×[5]								
India	×		×	×	×	×	×	×	×	×
Indonesia									×	×
Iran	×				×	×				s
Iraq	×	s[6]	×	×	×	×			×	s
Ireland	×		×	×	×	×			×	
Israel		×	×		×		×		×	×

Country	* Protocol of 11 December 1946	* International Opium Convention of 1912	* International Opium Convention of 19 February 1925, as an ended	* International Opium Convention of 19 February 1925	* Convention of 13 July 1931, as amended	* Convention of 13 July 1931	* Convention of 26 June 1936, as amended	* Convention of 26 June 1936	* Protocol of 19 November 1948	Protocol of 23 June 1953
Italy	×	×	×	×	×	×			×	×
Japan	×	×	×	×	×	×	×		×	×
Jordan (Hashemite Kingdom of the)					×	×[7]				
Laos		×[8]	×[8]		×[8]		×		×[8]	
Lebanon	×	×[9]	×		×				×	s
Liberia	×	×							s	
Libya										
Luxembourg	×	×	×	×	×	×	×		×	×
Malaya (Federation of)[10]										
Mexico	×	×			×	×r	×		×	
Morocco			×[11]		×[11]				×[11]	
Nepal										
Netherlands	×	×	×	×	×	×			×	s
New Zealand	×	×	×	×	×	×			×	×
Nicaragua	×	×			×	×			s	
Norway	×	×	×	×	×	×			×	
Pakistan									×	×
Panama	×	×			×	×			s	×
Paraguay	s	×		×		×			s	
Peru	s	×				×			s	
Philippines	×				×				×	×
Poland	×	×	×	×	×	×			×	
Portugal		×		×		×r				
Romania		×		×		×		×	s	
Saudi Arabia	×	×			×	×			×	
Spain	×	×	×	×	×	×			×	×
Sudan				×[12]		×[12]				
Sweden	×	×	×	×	×	×			×	
Syria	×	×[13]	×		×					
Thailand	×	×r	×	×	×	×r				
Tunisia										
Turkey	×	×	×	×	×	×	×	×	×	s
Ukrainian SSR	×								s	
Union of South Africa	×	×	×	×	×	×			×	s
USSR	×		×	×	×	×			×	
United Kingdom	×	×r	×	×	×	×			×	s
United States of America	×	×			×	×r			×	×
Uruguay	s	×		×		×			s	
Venezuela	s	×		×		×			s	s
Yemen									×	
Yugoslavia	×	×	×	×	×				×	s
Non-member states										
Germany (Federal Republic of)										s
Korea (Republic of)										s
Liechtenstein	×	×[14]	×	×[14]	×	×[14]			s	s
Monaco	×	×	×	×	×	×			×	×
San Marino				×		×			s	
Switzerland	×	×r	×	×	×	×	×		×	×
Vatican City (Holy See)										
Viet Nam		×[15]	×[15]		×[15]				×[15]	s

[1] Upon the signature of each of these treaties it was stated by the representative of the United Kingdom that, if ratified, they would apply, among others, to British India. Burma was then a part of India, wherefrom it was separated on 1 April 1937. Ratifications or accessions recorded by the United Kingdom Government on behalf of India before 1 April 1937 were thence to be considered as binding upon Burma.

[2] By joint notification received from the Governments of Cambodia and France on 3 October 1951, notice was given of the transfer of functions by the French Government to the Government of Cambodia and of the duties and obligations arising from the application of these conventions in the latter country.

[3] The participation of Ceylon was established by virtue of notice to that effect given by the Government of the United Kingdom on 18 May 1936, in accordance with article 26, second paragraph, of the Convention.

[4] The position of Ghana in connexion with its participation in the narcotics control treaties is under study, in consultation with the Government of Ghana.

[5] The signature of the Protocol of Signature of the Powers not represented at the 1912 Conference, as well as its ratification, were given by Denmark for Iceland; the signature of the Protocol respecting the putting into force of the Convention was given separately by Denmark and Iceland.

[6] The United Kingdom signed this Convention for Iraq on 20 October 1924.

[7] The participation of the Hashemite Kingdom of the Jordan was established by notice by the Government of the United Kingdom on 24 August 1938 as applicable to Transjordan.

[8] By joint notification received from the Governments of France and Laos on 7 October 1950, notice was given of the transfer of functions by the French Government to the Government of Laos and of the duties and obligations arising from the application of these conventions and protocol in the latter country.

[9] By a communication received on 24 May 1954, the Government of Lebanon notified the Secretary-General that it considered itself bound by the provisions of this convention.

[10] The position of the Federation of Malaya in connexion with its participation in the narcotics control treaties will be the object of consultations with the government of that country.

[11] On 7 November 1956 the Government of Morocco deposited with the Secretary-General a declaration stating that it considered itself bound by these treaties.

[12] Accession of the Sudan to the 1925 and 1931 Convention took place on 20 February 1926 and 25 August 1932 respectively.

[13] By a communication received on 20 January 1954, the Government of Syria notified the Secretary-General that it considered itself bound by the provisions of this convention, as amended by the 1946 Protocol.

[14] By communications of 15 July and 14 October 1936, the Government of Switzerland stated:

"Under the terms of the arrangements concluded between the Government of the Principality of Liechtenstein and the Swiss Government in 1929 and 1935, in application of the Customs Union Treaty concluded between these two countries on March 29th, 1923, the Swiss legislation on narcotic drugs, including all the measures taken by the Federal authorities to give effect to the different international Conventions on dangerous drugs, will be applicable to the territory of the Principality in the same way as to the territory of the Confederation, as long as the said Treaty remains in force. The Principality of Liechtenstein will accordingly participate, so long as the said Treaty remains in force, in the international Conventions which have been or may hereafter be concluded in the matter of narcotic drugs, it being neither necessary nor advisable for that country to accede to them separately."

[15] By joint notification received from the Governments of France and Viet Nam on 11 August 1950, notice was given of the transfer of functions by the French Government to the Government of Viet Nam and of the duties and obligations arising from the application of these conventions and protocol in the latter country.

Twelfth session of the Commission on Narcotic Drugs

The Commission on Narcotic Drugs met in New York from 29 April to 31 May 1957. It elected as officers:

Mr. H. J. Anslinger (USA), Chairman

Mr. D. Nikolic (Yugoslavia), Vice-Chairman

Mr. A. G. Ardalan (Iran), Rapporteur

The main items on the agenda were the following: the implementation of the narcotics treaties and international control; the illicit traffic; drug addiction; opium and opiates, including the request of Afghanistan to be recognized as a state producing opium for export, scientific research on opium, and the question of diacetylmorphine; the question of the coca leaf; the question of cannabis; the question of synthetic narcotic drugs; the problem caused by barbiturates, tranquillizers and khat; the proposed United Nations Middle East Anti-Narcotics Bureau; and the question of technical assistance for narcotics control. The proposed Single Convention was dealt with at length, the Commission devoting an extra week to that item in accordance with the resolution taken by the Economic and Social Council at its twenty-second session.

The Commission decided to defer to its thirteenth session consideration of the proposed United Nations Middle East Anti-Narcotics Bureau.

In accordance with the elections carried out by the Council at its twenty-first session, the membership of the Commission now consists of the following governments: Austria, Canada, China, Egypt, France, Hungary, India, Iran, Mexico, Peru, Turkey, Union of Soviet Socialist Republics, United Kingdom, United States and Yugoslavia.

Representatives of Afghanistan, Bulgaria, Cambodia, Denmark, Ethiopia, Federal Republic of Germany, Greece, Indonesia, Israel, Italy, Japan, Laos, Lebanon, Morocco, Pakistan, Poland, Portugal, Switzerland, Thailand and Viet Nam participated as observers in the consideration of items of particular concern to them. Representatives of the World Health Organization, the Permanent Central Opium Board, the Drug Supervisory Body, the Permanent Anti-Narcotics Bureau of the League of Arab States; and of the International Criminal Police Organization, the International Conference of Catholic Charities, the International Federation of Women Lawyers, the Pan-Pacific South-East Asia Women's Association, the World Alliance of Young Men's Christian Association, the World Women's Christian Temperance Union and the International Council of Nurses (R) also took part in the work of the Commission.

The Commission took a number of decisions, the principal of which are mentioned below, and recommended resolutions to the Economic and Social Council dealing with scientific research on opium, the question of khat and technical assistance for narcotics control which are noted under the next heading (twenty-fourth session of the Economic and Social Council).

Implementation of Treaties and International Control

The Commission, after studying the "Annual Summary Tabulation — Changes in the Scope of Narcotics Control in 1956", considered that national legislation or administrative measures promulgated during the year reflected a satisfactory awareness on the part of governments to carry out their obligations in this respect.

The Commission observed that two new synthetic drugs had been placed under international control during the year — namely, α-1-methyl-3-ethyl-4-phenyl-4-propionoxypiperidine and 1-[2-(p-aminophenyl)-ethyl]-4-phenylpiperidine-4-caboxylic acid ethyl ester and their respective salts. Upon being informed of the dangerous addiction properties of another new synthetic drug, R.875, the Commission took action, pursuant to article 2 of the 1948 Protocol, to place this drug provisionally under the control of the stricter regime laid down in the 1931 Convention, pending a final decision in this respect.

Illicit Traffic

In accordance with the established procedure, the Committee on Illicit Traffic met three working days in advance of the regular session and considered in closed meetings all the available information relating to the illicit traffic. The Committee's report to the Commission (document E/CN.7/L.145) was adopted, with minor amendments, by the latter as part of its own report to the Council.

The Commission drew attention to the basic features of the illicit traffic — namely, that it was supplied almost entirely from illicit sources, was well organized, and had widespread international ramifications. In this connexion, it adopted a resolution urging closer international co-operation against the activities of traffickers and stricter control by the national authorities concerned.

Opium and opiates were still by far the most important drugs involved in the internal and international traffic; a number of clandestine factories for the manufature of opiates had been discovered during the year. The traffic in cannabis was observed to be increasing all over the world. The traffic in cocaine, though at a low level, was still persistent. Seizures of synthetic drugs in small amounts continued to be reported.

Finally, the Commission reviewed the performance of obligations relating to the exchange of information on illicit traffic pursuant to treaty obligations. It appealed to all governments for strict fulfilment of these obligations in view of the world-wide character of the illicit traffic and evidences of an increase in activities of traffickers.

Drug Addiction

The Commission noted that, despite ample evidence of a growing awareness of the addiction problem and of increasing efforts to combat it, some countries had reported more addicts for 1955 than for 1954. Close estimates of the extent of addiction, however, could not be made owing to the varying degrees in which addiction was known to the authorities in various countries.

The Commission considered in particular the discovery, registration and control of addicts, their treatment and rehabilitation and preventive measures that might be taken to reduce their number. These aspects of the problem were

examined mainly in the light of the analytical study on drug addiction (E/CN.7/318) prepared by the Secretary-General. In connexion witht the treatment of addicts, a report of the World Health Organization's Study Group on Treatment and Care of Drug Addicts (E/CN.7/320) was also considered.

The Commission learned from several of its members and observers that their countries were expanding facilities for the treatment of addicts. The Commission was generally in agreement with the treatment measures proposed by the World Health Organization's Study Group and expressed the hope that the work on this subject would be continued. It further requested the Secretariat to obtain additional information on addiction from certain countries.

The Proposed Single Convention on Narcotic Drugs

In accordance with Council resolution 246 D (IX), the Commission on Narcotic Drugs proceeded with its work of codifying the treaty law on narcotic drugs. It used as a working paper the second draft of the proposed Single Convention on Narcotic Drugs (E/CN.7/AC.3/7 and Corr.1), which had been prepared in accordance with decisions taken by the Commission from 1950 to 1955. It had also before it an analytical compilation of comments from twenty-four governments (E/CN.7/AC.3/8 and Add.1 and 2).

The Commission prepared a revised and considerably simplified and shortened text for twenty-four out of sixty articles of the second draft. It arranged for differing viewpoints to be reproduced in footnotes to the text.

In this process, it settled several important questions. In particular, decisions taken by the Commission under the new text to prohibit particularly dangerous narcotics without compensating therapeutic advantages would be legally binding upon parties to the Convention. In general, however, in order to expedite its work, the Commission avoided reconsidering questions of principle which it had decided at earlier sessions.

The Question of Diacetylmorphine

The Commission reviewed the present situation in connexion with the implementation of the resolutions of the Economic and Social Council (548 G (XVIII)), the Sixth World Health Assembly and the Commission at its tenth session, recommending in varying degrees the prohibition of diacetylmorphine. Document E/CN.7/317/Add.1, a part of the Report of the Division, giving all the available information on the subject, was examined. The Commission noted that out of eighty-seven countries considered, which included all the Members of the United Nations, sixty-three had either prohibited diacetylmorphine or had adopted a policy of prohibition, and that nineteen had not yet done so either in practice or by a declaration of policy, there being no available information on the remaining ones. The Commission decided to request the Secretariat to prepare an annual supplementary return on this matter.

Scientific Research on Opium

With regard to the operation of the United Nations laboratory in Geneva, the opium samples for research and distribution to collaborating chemists assembled prior to the establishment of the laboratory had been received in Geneva from New York, as well as numerous further samples transmitted by governments. Alkaloidal and related analyses were being made; work on developing methods of determining constituents of opium by chromatography, electrochromatography and electrophoresis was being carried out, and spectrophotometric and flame photometric analyses to determine major elements in opium had been commenced.

The programme of international collaboration had continued. A total number of 343 authenticated samples had been received from fourteen countries, and twenty-four other samples from six countries. Several technical papers by scientists of several countries dealing with research on opium were issued. Opium samples for study had been sent to scientists in several countries.

The Commission expressed satisfaction at the inauguration of a fellowship programme in this field with the arrival of a student from Singapore to work in Canada in November 1956.

The Comission took notice of the forthcoming meeting of experts pursuant to Council resolution 626 (XXII). It adopted a resolution giving priority to work on authenticated samples in the laboratory.

The Question of the Coca Leaf

The representative of Peru informed the Commission of the efforts being made by his country directed towards limiting the production of the coca leaf, reducing the number of chewers, controlling exports of the leaf, and strengthening the administrative machinery in these respects. The production of the coca leaf had somewhat decreased in 1956, and no new licences for the cultivation had been issued in that year. The problem of the chewing of the coca leaf was complicated by the fact that most of the addicts lived in poor agricultural areas where malnutrition and alcoholism raised additional problems. There were approximately 1½ million habitual chewers who, on an average, consumed 10 kg of coca leaves each per year. The Peruvian Government had strengthened the legislation governing exports of the coca leaf, and was contemplating an increase in the export duty on them. That government regretted that importing countries did not import more crude cocaine instead of coca leaves, as had been suggested in an earlier resolution of the Commission. The Commission discussed whether the export of crude cocaine manufactured in Peru rather than of coca leaves would, in fact, contribute to the closer control of that drug internationally.

Dr. J. Haaker, the Minister of Public Health of Peru, addressed the Commission on the question of the coca leaf and the prospects for ameliorating the situation.

The Commission observed that the Government of Chile had recently drafted legislation providing for the prohibition of coca leaf chewing, and that the Government of Argentina had declared such chewing to be harmful, and had taken action in 1956 regarding the import of the coca leaf.

The Question of Cannabis

In considering the problems arising out of the use of the drug cannabis, known locally by a great variety of names such as marihuana, kif, ganja, bhang, etc., the Commission was informed of recent progress in India towards the reduction and elimination of the medical and non-medical use of cannabis, and of the banning of cultivation, consumption and use of cannabis in Morocco. The situation in Egypt was also described to the Commission. In that country, the cultivation and consumption of cannabis are prohibited; there is, however, an illicit consumption, hashish being

smoked with tobacco, drunk as an infusion in tea or coffee, and eaten in chocolate or pastries. The question of the breeding of a narcotic-free strain of the cannabis (Indian hemp) plant, the difficulties caused by the fact that the plant grows wild, and the complete lack of therapeutic value of cannabis drugs were also considered.

The Commission adopted a resolution which, *inter alia*, requests all governments to abolish the legal consumption of cannabis except for medical and scientific purposes (cannabis is still used in the indigenous Ayurvedic, Unani and Tibbi systems of medicine), and invites governments to promote research in order to find out what is the active principle, or what are the active principles of cannabis, their exact nature never having been fully established.

The Question of Synthetic Narcotic Drugs

The Commission again discussed the problems arising from the continuing increase of the number of substances under international control and in general medical use. It considered the fourth and last of the studies on morphine-like substances, prepared under Council resolution 505 C (XVI) by the World Health Organization in conjunction with the United Nations Secretariat, which dealt with the relative addictive properties and therapeutic advantages of natural and synthetic narcotics respectively. It was informed that at least one strong analgesic free of addiction liability had been developed, although its use in medicine was limited by its side-effects.

In view of the importance of this and related questions and the steady increase of available data, the Commission recommended that a research programme in this field should be carried out over a number of years, with the World Health Organization, the Permanent Central Opium Board and Drug Supervisory Body, and the International Criminal Police Organization collaborating in the studies falling within their respective provinces.

The Commission also invited governments to extend to synthetic narcotics the measures for tightening control over their manufacture and distribution which it had recommended at its eleventh session in respect of natural narcotics.

The Question of Ketobemidone

Considering a request by the Government of Switzerland, the Commission decided not to change its position on ketobemidone. It found that there was no reason to revise the conclusion that ketobemidone had " particularly dangerous properties ", which had led the Council at its eighteenth session to recommend, on the initiative of the Commission, the prohibition of the manufacture, import and export of ketobemidone, its salts and preparations and preparations of its salts.

Use of Non-proprietary Names for Narcotic Drugs under International Control

The Commission again considered the possibility of shortening the procedure for giving narcotic drugs international non-proprietary names. The matter has assumed importance because of the rapid increase in the number of drugs being manufactured, the complexity of the names, and the large number of trade names for certain drugs.

The Commission examined the present procedure and requested further study in co-operation with the World Health Organization of the possibility of simplifying it and the drafting of relevant provisions for inclusion in the Single Convention.

The Question of Barbiturates and Tranquillizers

The Commission considered the difficulties that had arisen in various countries as the result of the increasing use of barbiturates and tranquillizers, and the action that could be taken at the international level in this regard. It received information from several of its members and observers as regards regulations at present in force in their countries, and decided to recommend to governments to take the appropriate legislative and administrative measures of control to prevent the abuse of barbiturates and to keep a careful watch for any abuse of the substances described as " tranquillizers " or " ataraxic " drugs, with a view to taking any necessary measures of control.

Twenty-fourth session of the Economic and Social Council

At its twenty-fourth session, held in Geneva from 2 July to 2 August 1957, the Council considered and took note of the Reports of the Commission on Narcotic Drugs on its twelfth session and of the Permanant Central Opium Board on the Work of the Board in 1956.

The Request of Afghanistan to be recognized as a State producing Opium for Export

In pursuance of Council resolution 626 G (XXII), the Commission had considered further the request of Afghanistan to be recognized as a state producing opium for export. The Commission, noting that Afghanistan had become a party to the 1925 Convention and had in other ways demonstrated its readiness to carry out obligations of international narcotics control, had postponed action until its thirteenth session, at which time it hoped to have further information on the development of the questions involved. The Governments of Afganistan and Iran were to be invited to furnish all available information on these questions. The Commission had pointed out that since the 1953 Protocol was not yet in force, Afghanistan as yet required no permission to produce and export opium for medical and scientific purposes. The Council had before it communications from Afghanistan and Iran. The Council discussed the position in the light of these communications without, however, adopting a further resolution on the question.

Scientific Research on Opium

The Council considered this subject on the initiative of the Commission on Narcotic Drugs and adopted resolution 667 C requesting the Secretary-General to increase the resources of the United Nations laboratory in order to permit the making of an increased number of analyses of opium samples, and the expediting of research on methods of determination of origin by physical and chemical means.

The Question of Khat

The Council, on the recommendation of the Commission, adopted resolution 667 D, noting that the habitual chewing of the leaves of khat had become wide-spread in several countries, recognizing that this habit gave rise to a grave social problem in the countries affected, and inviting the World Health Organization to study the medical aspects of the problem.

Draft Single Convention on Narcotic Drugs

In accordance with the Commission's suggestion, the Council adopted resolution 667 E (XXIV) granting the Commission authority to sit an additional week during its thirteenth session for the purpose of advancing more speedily its work of codification.

Technical Assistance for Narcotics Control

The Commission considered that an encouraging start had been made in aid to Iran in the field of narcotics as had been provided under the Expanded Programme of Technical Assistance of the United Nations and the specialized agencies. It was informed that other countries, notably India and Morocco, intended to apply for help in combating illicit traffic, in the rehabilitation of addicts and in eradicating the wild growth of the cannabis plant and other problems connected with international control of narcotic drugs. The Commission received an offer from the International Criminal Police Organization to place its services and facilities at the disposal of the Technical Assistance Programme to train police personnel in anti-narcotic work.

On the invitation of the Commission, the Council adopted a resolution 667 F (XXIV), by which it drew attention to the importance of measures being taken in India and Morocco to deal with the problem of cannabis, and invited the technical assistance authorities of the United Nations and the specialized agencies to give due consideration to any requests for assistance within the framework of the existing administrative and financial arrangements which they might receive from the governments of those countries.

Technical Assistance to Iran

The Council, in its resolution 626 E (XXII), had affirmed that, in order to ensure the execution of the law bannind cultivation of the opium poppy, Iran required increaseg technical assistance in enabling its cultivators to introduce other agricultural crops to replace opium poppy plantation, and also in respect of the treatment of addicts. It recalled that at its twelfth session the Commission on Narcotic Drugs expressed its appreciation of the considerable progress that had been made in Iran in this regard, and adopted a resolution requesting the Technical Assistance Board and the participating organizations concerned to continue to give due consideration to requests by the Government of Iran for technical assistance in this field; and requesting further that the Secretary-General, after consultation with the participating organizations concerned, report to the Commission on Narcotic Drugs and to the Council on the extent to which it has been possible to meet the request of Iran for technical assistance in this regard.

The Question of inviting the Authorities entitled to appoint Members of the Supervisory Body to appoint Persons who are also Members of the Board

The Council, in order to ensure to the greatest possible extent close liaison and personal union between the Permanent Central Opium Board and the Drug Supervisory Body pending the establishment and coming into effect of a single convention, adopted a resolution 667 H (XXIV), by which it invited the World Health Organization, the Commission on Narcotic Drugs and the Permanent Central Opium Board to consider appointing persons who are members of the Board to the Drug Supervisory Body for a five-year period corresponding to the term of office of members of the Board provided for in the 1925 Convention.

CORRIGENDA TO VOLUME VIII

VOLUME VIII, No. 1

Page 21, left-hand column: 2. Opium, sub-paragraph (2), Benzylisoquinoline derivatives, second line: Instead of " $C_{22}C_{23}O_7N$ ", the formula should read " $C_{22}H_{23}O_7N$ ".

Page 23, Table III, Derivatives of Opium Alkaloids, formula (III-5): Instead of " Dilandid ", read " Dilaudid ".

VOLUME VIII, No. 2

Page 14, left-hand column, line 15: Instead of "Convention signed at Geneva on 13 February 1925 ", read " Convention signed at Geneva on 19 February 1925 ".

Page 18, right-hand column, line 28: Instead of " dithienylbutenylamine and its derivates ", read " dithienylbutenylamine and its derivatives ".

VOLUME VIII, No. 3

Page 3, left-hand column, footnote 1, first line: Instead of " Senate Report 4440 ", read " Senate Report 1440 ".

Page 14, right-hand column, fourth paragraph, first line: Instead of " The committee is convinced ", read " The sub-committee is convinced ".

Page 23, left-hand column, between sub-paragraph (*t*) and sub-paragraph (*o*) there should be inserted the following: " Sec. 3. Section 301 of such Act (21 U.S.C. 331) is amended by adding at the end thereof the following: "

Page 28, right-hand column, penultimate line: Instead of " World consumption of pethidine in 1950 ", read " World consumption of pethidine in 1954 ".

Page 29, left-hand column, tenth paragraph, fourth line: Instead of " prescriptions of synthetic drugs ", read " prescriptions of narcotic drugs ".

Page 38, right-hand column, first line: Instead of " This is confirmed by Wisner ", read " The same conclusion was reached by Wisner ".

Page 41, right-hand column, reference No. 20: " ANNET " should be spelt " ANNETT ".

Page 41, right-hand column, reference No. 21: Instead of " HENRY, J. ", the initials should be " HENRY, T. A."

VOLUME VIII, No. 4

Page 45, left-hand column, penultimate line: Instead of " of cultivation of the opium ", read " of cultivation of the opium poppy ".

Page 47, right-hand column, footnote ★, second line: Instead of " H. L. Moy ", read " H. L. May ".

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